BMJ: Therapeutics

Therapeutics: Disease-modifying therapies for multiple sclerosis

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A 32-year-old woman with multiple sclerosis (MS) presents to her GP with a five-day history of numbness and weakness in the right leg. She feels well in herself and does not describe any symptoms to suggest an intercurrent infection. She has been taking weekly intramuscular injections of interferon-β1a for the last 18 months and reports flu-like symptoms that can last for up to 24 hours after each dose. She asks if there is a need to change her treatment and what alternatives are available.

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating disorder of the central nervous system affecting over 2 million people worldwide.[1] It is a major cause of physical disability in young adults and has profound implications for cognition, emotional well-being and employment. Patients commonly present with unilateral visual loss (due to optic neuritis), double vision, sensory symptoms, limb weakness or imbalance.[2] The diagnosis is based on clinical features and MRI findings, sometimes supported by lumbar puncture and other investigations.[2, 3]

Nearly 80-85% of people with MS experience a relapsing course with episodes of new or worsening neurological symptoms lasting at least 24 hours followed by full or partial recovery, in the absence of fever or infection (attacks or relapses).[3] Untreated, most people with relapsing MS develop disability over time due to incomplete recovery from relapses, or a change in disease course to progressive MS, with a steady increase in disability. In 10-15% of people with MS, the disease is progressive from onset (primary progressive MS [PPMS]). [Box 1]

What treatments are available for MS?

Currently, 15 disease-modifying therapies (DMTs) are licenced for relapsing MS, including five preparations of interferon-β and three preparations of glatiramer acetate [2, 4]. A number of oral and monoclonal antibody therapies for MS have become available in the last decade (Figure 1). Ocrelizumab [5], the first treatment for PPMS, has recently been licenced.

The DMTs have varying mechanisms of action (Supplementary Box) with immunosuppressive and immunomodulatory effects that target:

- lymphocyte number (alemtuzumab, ocrelizumab, cladribine);
- lymphocyte proliferation (teriflunomide, mitoxantrone);
- lymphocyte trafficking (fingolimod, natalizumab);
- cytokine production (interferon-β, glatiramer acetate).

According to the regulatory agencies licencing, DMTs may have different indications (Box 1).

International guidelines on starting, switching and stopping DMTs in people with MS (Box 2) recommend offering DMTs to patients with active relapsing MS. [6–8] No treatment is advised for patients with inactive MS [8]. The ECTRIMS/EAN and AAN guidelines recommend offering interferon-β or glatiramer acetate in patients with a clinically isolated syndrome, i.e. the first episode of neurological symptoms suggestive of MS with brain MRI abnormalities (indicating a high-risk of MS), to delay the second attack, and ocrelizumab in patients with PPMS.[6, 7]

How well do they work?

There is moderate to high quality evidence from phase III randomised controlled trials and systematic reviews [9, 10] that DMTs reduce the relative risk of developing relapses (Table 1), accumulation of new brain MRI lesions, and disability progression over 2-3 years in active relapsing MS, compared with placebo, or an active comparator (interferon-β).[4] The use of relative measures over absolute measures is preferred to compare the efficacy of two treatments in MS because the former appear to be more stable across populations of patients with different relapse and MRI measures of disease activity. [11, 12] When recommending starting a DMT, a clinician might discuss with the patient that being on that medication – rather than being on no medications at all - will reduce the risk of developing relapses by a certain percentage as found in large clinical trials (Table 1). DMTs generally do not improve established symptoms of MS, although a pivotal trial [13] showed that alemtuzumab treated patients were more than twice as likely as interferon-β treated patients to experience 6-month confirmed disability improvement (28.8% vs 12.9%, Hazard Ratio [HR]= 2.57, p=0.0002), and a post-hoc study from another pivotal trial showed that natalizumab [14] improved disability by 69% (HR = 1.69; 95% Confidence Intervals [CI] 1.16–2.45; $p = 0.006$) versus placebo in a subset of patients with baseline expanded disability status scale scores ≥ 2.0.

Clinical trials in MS are typically of 2-3 years duration and the long-term benefits of DMTs are uncertain. Observational studies report conflicting evidence on the impact of interferon-β in reducing long-term disability and development of secondary progressive MS [15, 16].

Few studies have directly compared different DMTs. A systematic review of head-to-head trials (including 5 randomised controlled trial and 2858 participants) comparing interferon-β preparations and glatiramer acetate found a similar effect on relapses and disability progression, although secondary MRI endpoints favoured interferon-β. [17] In separate phase III randomised controlled trials, interferon-β had similar efficacy to teriflunomide, and was less effective than fingolimod, alemtuzumab and ocrelizumab. A Cochrane network meta-analysis in 2015 (including 39 randomised controlled trials and 25,113 participants) looked at the efficacy of 15 DMTs (including three different preparations of interferon-β). It found that, over a 24-month period, alemtuzumab (risk ratio [RR] versus placebo 0.46, 95% CI 0.38-0.55), natalizumab (RR 0.56, 95% CI 0.47-0.66), and fingolimod (RR 0.72, 95% CI 0.64-0.81) were more effective for preventing relapses based on moderate to high-quality evidence, and natalizumab (RR 0.64, 95% CI 0.49-0.85) was more effective for preventing disability worsening based on moderate quality evidence. [9] The main limitations of this review were that the majority of the incuded studies were sponsored by pharmaceutical companies and had a short duration in time (median 24 months). Since the publication of this Cochrane review, new clinical trials in relapsing MS have been reported.[5, 18, 19] In 2017, a network meta-analysis (including 33 studies and 21,768 participants with relapsing MS) was carried out by the US Institute for Clinical and Economic Review on 16 DMTs including 5 formulations of interferon-β and 3 of glatiramer acetate and the newly approved ocrelizumab (not reported in the Cochrane review). The analysis showed that, between the FDA licenced drugs for relapsing MS, alemtuzumab, natalizumab, and ocrelizumab had the greatest reduction in the annualised relapse rates (approximately 70% reduction compared to placebo), fingolimod, and dimethyl fumarate were the next most

effective (47% to 54% reduction) and the interferons, glatiramer acetate and teriflunomide were less effective (17% to 37% reduction). This analysis is limited by the short-term follow-ups of the included studies and the lack of head-to-head trials. Furthermore, it pointed out that the evolving MS diagnostic criteria over the past 2 decades have caused important variation among the studied patient populations across trials.

What are the harms?

Very common (≥10% of patients) or common (≥1% to <10% of patients) adverse reactions of DMTs, as reported in the relevant summaries of product characteristics, include: flu-like symptoms (interferon-β); headache (interferon-β, fingolimod); gastrointestinal upset (dimethyl fumarate, teriflunomide); injection site reactions (interferon-β, glatiramer acetate). These are generally mild but can impact on adherence, and sometimes require a change of treatment. Infusion reactions occur commonly with alemtuzumab and ocrelizumab.

Interferon-β and glatiramer acetate have an excellent long-term safety profile, as shown by long-term observational studies.[20–22] The oral and monoclonal antibody treatments for MS can have serious adverse reactions including opportunistic infections, cardiac arrhythmias, hepatotoxicity and secondary autoimmunity (Table 1), and the long-term safety profile of these DMTs is unknown. Daclizumab, an anti-CD25 monoclonal antibody, has recently been withdrawn following cases of severe liver injury and immune-mediated encephalitis not observed in phase III clinical trials. Post-authorisation safety studies and pharmacovigilance are essential for all newly approved DMTs, and can lead to marketing authorisation changes by the regulatory

agencies. DMTs may be associated with serious adverse reactions (see below). Natalizumab and alemtuzumab are subject to a Risk Evaluation and Mitigation Strategy (REMS) by the FDA, requiring training and support for healthcare providers to monitor patients during treatment to reduce the occurrence and/or severity of serious risks.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML), due to reactivation of the John Cunningham virus (JCV), is an opportunistic brain infection that can complicate treatment with natalizumab and is associated with high rates of death or disability. JCV serostatus and antibody index should be checked before starting natalizumab (and periodically during treatment) to stratify PML risk. PML has rarely been reported in patients with fingolimod (estimated risk <1:10,000) and dimethyl fumarate who have not been treated with natalizumab.

Cardiac arrhythmias

Fingolimod causes first-dose bradycardia (~1-2%), and rarely transient heart block (<0.5%). An electrocardiogram should be obtained prior to starting treatment and the first dose administered with heart rate monitoring for 6 hours after the first dose. Cases of ventricular tachycardia and sudden cardiac death have also been reported with fingolimod. Fingolimod should be avoided in patients with a history of ischemic heart disease or cardiac arrhythmias.

Hepatotoxicity

Deranged liver function tests (LFTs) commonly occur with a number of DMTs (particularly interferon-β, dimethyl fumarate, fingolimod). Individual cases of fatal liver injury have been reported with leflunomide (the pro-drug of teriflunomide). Teriflunomide should be avoided in people with a history of liver disease.

Secondary autoimmunity

Autoimmune thyroid disease, immune thrombocytopenic purpura and glomerulonephritis may occur in people treated with alemtuzumab, most often in the second or third year after starting treatment (risk of secondary autoimmunity ~50% at 5 years).

Malignancy

DMTs should not be prescribed in patients with an active malignancy, and the safety in patients with a history of cancer is uncertain. Fingolimod is associated with an increased risk of skin cancers, particularly basal cell carcinoma. Mitoxantrone is associated with an increased risk of acute myeloid leukaemia (0.5-1%), and possibly solid-organ cancers. The long-term risk of cancer with other DMTs is unknown.

How are they given and monitored?

DMTs are prescribed and monitored in secondary care, often through specialist MS clinics with neurologists, nurse specialists and pharmacists. The route

(subcutaneous or intramuscular injection, oral, intravenous) and frequency of administration differs by the drug. A discussion of the risks and benefits of treatment is important. Figure 2 lists important considerations when selecting DMTs. Blood monitoring is required for all DMTs (except glatiramer acetate), particularly full blood count (to detect lymphopenia) and liver function tests. The frequency and type of blood test and other monitoring, such as brain MRI or urine test, are mandated by regulatory authorities (Table 1 and Tips for safer prescribing Box).

Most DMTs require ongoing treatment, with return of disease activity if the drug is interrupted or stopped. Some DMTs have immune-reconstitution properties with sustained effects on relapse rates and MRI activity in the absence of ongoing treatment (alemtuzumab, cladribine). Adherence to treatment is important and DMTs may be changed in patients with side-effects. There is no guidance on stopping treatment; this is usually decided by the treating neurologist in discussion with the patient based on the response and side effects (Figure 2).

Periodic clinical reviews to check for relapses and/or disability progression plus MRI scanning are used to monitor response to treatment. Evidence of disease activity on MRI is associated with an increased risk of disability progression, even in patients who are stable clinically [23, 24]. Some neurologists use the target of “no evidence of disease activity” (NEDA) when treating relapsing MS, recommending a change of treatment if there are ongoing relapses, new MRI activity or disability progression [25]. There is conflicting evidence on the benefits of this approach [26, 27].

How cost-effective are they?

DMTs account for over half of direct medical costs in people with MS.[28] There is wide variation in the cost of DMTs between countries. The cost of DMTs has increased dramatically in the United States over the last 10 years with 10-15% increase annually. The annual cost of most DMTs now exceeds US$70,000/year. [28] A number of studies have found that DMTs are not cost-effective at accepted economic thresholds. [28] A recent analysis from the Institute of Clinical and Economic Review found that among the currently available DMTs, alemtuzumab may be most cost-effective because of the combination high-efficacy and unique dosing strategy (two cycles of treatment over 2 years with further treatment given only if needed).[10] Lower drug pricing (as in the United Kingdom [29]), the availability of generics [30], off-label prescribing (e.g. rituximab [31]), and the increasing use of DMTs that do not require ongoing maintenance treatment may improve cost-effectiveness.

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What you need to know

- People with active relapsing MS should be considered for DMTs early in the course to prevent relapses, new brain and spinal cord lesions and worsening neurological disability.
- Some DMTs are associated with potentially serious adverse reactions and careful monitoring is required, usually through a specialist MS clinic.
- Newer DMTs have higher efficacy than older DMTs, but there are insufficient data about their effectiveness and risks in the long-term.
- The first treatment for primary progressive MS has recently been approved.

Tips for safer prescribing

- DMTs are contraindicated in patients with active infections or malignancy, and in patients taking other immunosuppressants.[32]
- Fingolimod has interactions with CYP3A4 enzyme inhibitors (azole antifungals, macrolides antibiotics, protease inhibitors) and inducers (rifampicin, carbamazepine, St John's wort), and pharmacodynamic interactions with beta blockers and calcium channel blockers.
- Follow regulatory authority guidance on blood, urine and MRI monitoring requirements.
- MRI monitoring is mandatory in patients treated with DMTs associated with a risk of PML (natalizumab, fingolimod, dimethyl fumarate), on at least an annual basis, and every 3-6 months in natalizumab-treated patients at high-risk of PML.[33]

Pregnancy and breastfeeding

Women taking DMTs should be counselled to use effective contraception. DMTs are usually discontinued prior to conception, although interferon-β and glatiramer acetate may be safe during conception and pregnancy. [34] The EMA recently updated the label of branded glatiramer acetate (Copaxone®) to remove pregnancy as a contraindication. Teriflunomide is teratogenic and an accelerated elimination procedure may be required prior to conception because of its long half-life. Preconception planning to make decisions regarding DMTs and obstetric care should be considered in women with MS.[35]

Vaccinations

Live or live-attenuated vaccines should be avoided in patients taking most DMTs. Patients who are Varicella-Zoster virus IgG negative should be immunised, particularly before treatment with fingolimod or cladribine.[32]

Tips for patients

- Several disease-modifying therapies with moderate (30-50% reduced relapse rate) or high (>50% reduced relapse rate) efficacy are available for relapsing MS. Discuss the options with a specialist MS team to select the treatment that fits best with your preferences.
- DMTs do have potential side effects, some of which are serious.
- Almost all of the DMTs have monitoring requirements such as routine blood tests, but some treatments need more monitoring than others such as special blood tests, urine tests and brain MRIs. Your MS Team will explain to you what kind of monitoring you require.
- New symptoms might mean a change of DMT is required. Know how to contact your MS nurse specialist or neurologist if you have new or worsening symptoms between clinic visits.
- MRI scans are an important part of deciding how well DMTs are working. When was your last MRI?
- Some DMTs are unsafe for women who are pregnant or breastfeeding. If you are considering becoming pregnant, then discuss this with your MS team.

Education into practice

- Are all your patients with active relapsing MS referred to a neurologist for a discussion regarding DMTs?
- Are women you see who take DMTs using effective contraception?
- Consider placing an alert on the electronic patient record for people receiving DMTs so that complications of treatment are recognised promptly in patients presenting acutely in primary or secondary care.

How patients were involved in the creation of this article

We asked two patients who attend our specialist MS clinic to comment on the draft manuscript and develop the Tips for Patients section. They highlighted the importance of early referral to a specialist MS team, the importance of lifestyle factors and burden of monitoring when selecting DMTs, and contraception/preconception counselling in women with MS.

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FIGURE AND BOX LEGEND

Figure 1. Timeline of the approved disease-modifying therapies

The figure shows the timeline of the approved DMTs for relapsing MS according by the FDA (on the top) and the EMA (on the bottom).

DMT= disease-modifying therapy; EMA= European Medicines Agency; FDA= Food and Drug Administration; MS= multiple sclerosis.

± Daclizumab (Zynbrita®, Biogen) has been withdrawn from the market by Biogen in March 2018, due to cases of encephalitis and meningoencephalitis.

§ Glatiramer acetate was approved after Mutual Recognition Procedure in Europe (the UK was the reference member state) and not formally by the EMA. Glatiramer acetate (Copaxone®, Teva) was approved in the UK in 2000.

Mitoxantrone has been authorised in the EU via national procedures and not initially formally reviewed by the EMA. In 2016, the EMA was asked to harmonise the marketing authorisations in the EU. The EMA declared that Mitoxantrone is indicated for treatment of patients with highly active relapsing MS associated with rapidly evolving disability where no alternative therapeutic options exist.


(Syringe symbol) = Injectable drug


(Capsule symbol) = Oral drug


(Intravnous-drip symbol) = Intravenous drug

Figure 2. Factors influencing disease-modifying therapy choices in multiple sclerosis

Box 1. An approach to treating multiple sclerosis

The box shows an approach to treat relapsing MS according to the EMA, with a mention to the FDA indications. The EMA allows the prescription of some treatments (natalizumab, fingolimod, cladribine, mitoxantrone) to patients with highly-active MS. Of note, the FDA does not group patients according to disease activity (i.e. active or highly active) but rather on patients' response to DMTs (i.e. if patients develop relapses or new/enlarged or gadolinium enhancing lesions while on DMTs).

DMTs can only be prescribed by MS experts (secondary care). Standard care should be carried out by both primary and secondary care. References: Brownlee WJ 2017 [2] and Galea I 2015 [27].

Abbreviations: DMT= disease-modifying therapy; CIS= Clinically Isolated Syndrome; CNS= central nervous system; DMT= disease-modifying therapy; EMA= European Medicines Agency; FDA= food and Drug Administration; MRI= magnetic resonance imaging; MS= multiple sclerosis; PPMS= primary progressive multiple sclerosis; SPMS= secondary progressive multiple sclerosis; Std= Standard.

* The FDA allows the use of alemtuzumab only if patients have not had an adequate response to two or more of the other approved DMTs.

**Fingolimod is only approved first-line in Europe for highly active MS

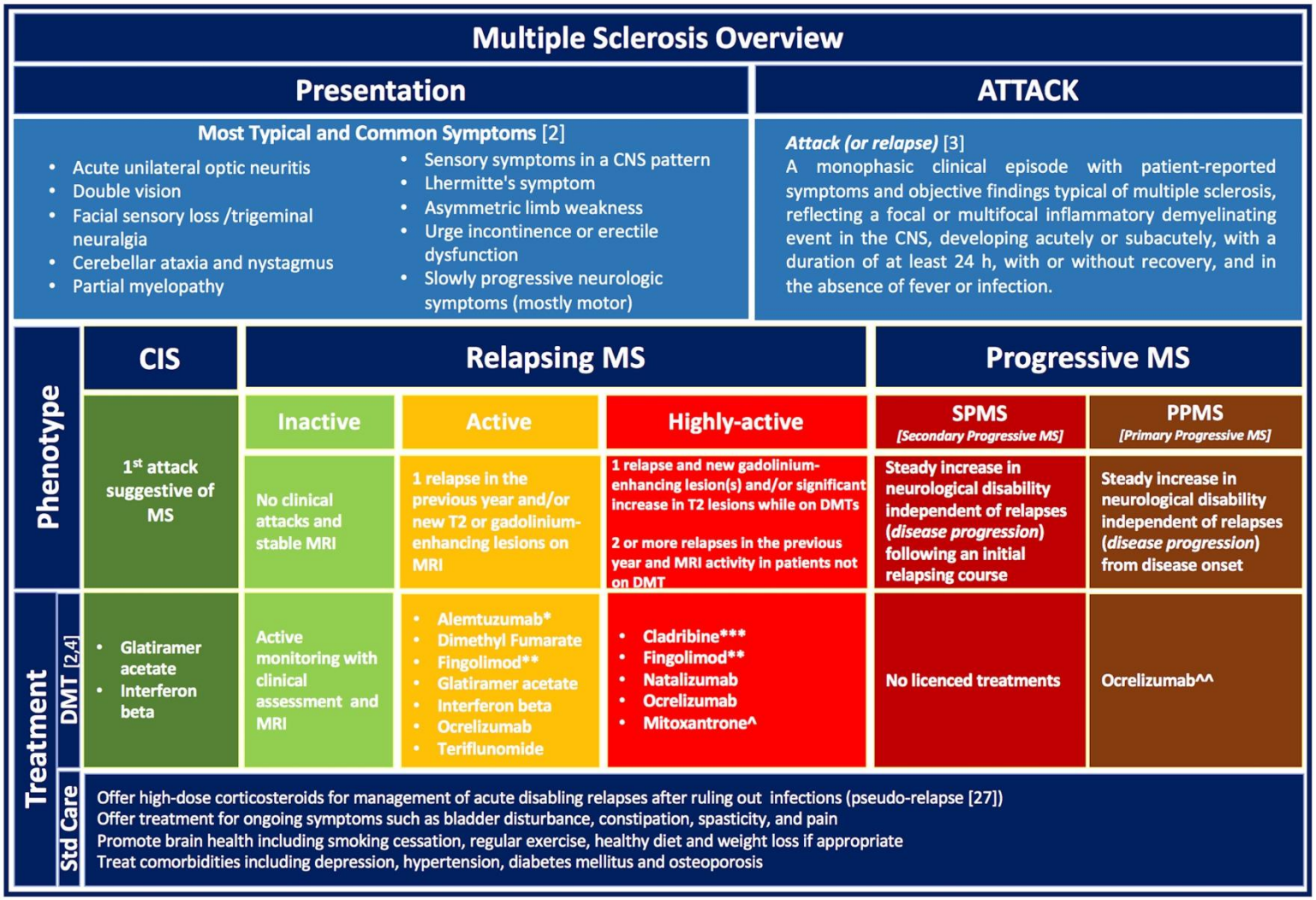
*** Cladribine is not approved by the FDA.

^ Mitoxantrone is approved by the EMA for treatment of patients with highly active relapsing MS associated with rapidly evolving disability where no alternative therapeutic options exist. The FDA allows the use of mitoxantrone only if patients have not had an adequate response to two or more of the other approved DMTs

^^Licenced for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Box 2. Overview of guidelines for starting, switching and stopping disease-modifying therapies

Abbreviations: ABN= Association of British Neurologists; AAN= American Academy of Neurology; CIS= clinically isolated syndrome. DMTs= disease-modifying therapies. EAN= European Academy of Neurology; ECTRIMS= European Committee for Treatment and Research in Multiple Sclerosis. JCV= John Cunningham virus. MS= multiple sclerosis. PPMS= primary progressive multiple sclerosis.


Multiple Sclerosis Overview
Presentation
ATTACK
Most Typical and Common Symptoms [2]
Acute unilateral optic neuritis
Double vision
Facial sensory loss /trigeminal neuralgia
Cerebellar ataxia and nystagmus
Partial myelopathy
Sensory symptoms in a CNS pattern
Lhermitte's symptom
Asymmetric limb weakness
Urge incontinence or erectile dysfunction
Slowly progressive neurologic symptoms (mostly motor)
Attack (or relapse) [3]
A monophasic clinical episode with patient-reported symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 h, with or without recovery, and in the absence of fever or infection.
Phenotype
CIS
Relapsing MS
Progressive MS
Inactive
Active
Highly-active
SPMS [Secondary Progressive MS]
PPMS [Primary Progressive MS]
1st attack suggestive of MS
No clinical attacks and stable MRI
1 relapse in the previous year and/or new T2 or gadolinium-enhancing lesions on MRI
1 relapse and new gadolinium-enhancing lesion(s) and/or significant increase in T2 lesions while on DMTs
2 or more relapses in the previous year and MRI activity in patients not on DMT
Steady increase in neurological disability independent of relapses (disease progression) following an initial relapsing course
Steady increase in neurological disability independent of relapses (disease progression) from disease onset
Treatment
DMT [2,4]
Glatiramer acetate
Interferon beta
Active monitoring with clinical assessment and MRI
Alemtuzumab*
Dimethyl Fumarate
Fingolimod**
Glatiramer acetate
Interferon beta
Ocrelizumab
Teriflunomide
Cladribine***
Fingolimod**
Natalizumab
Ocrelizumab
Mitoxantrone^
No licenced treatments
Ocrelizumab^^
Std Care
Offer high-dose corticosteroids for management of acute disabling relapses after ruling out infections (pseudo-relapse [27])
Offer treatment for ongoing symptoms such as bladder disturbance, constipation, spasticity, and pain
Promote brain health including smoking cessation, regular exercise, healthy diet and weight loss if appropriate
Treat comorbidities including depression, hypertension, diabetes mellitus and osteoporosis

Box 1

Box 2. Overview of guidelines for starting, switching and stopping disease-modifying therapies

	ECTRIMS/EAN Guidelines[6]	**AAN Guidelines**[7]	**ABN Guidelines**[8]
Starting DMTs	- Offer Interferon-β or glatiramer acetate in CIS patients with abnormal brain MRI - Offer DMTs in patients with active relapsing MS - Consider treatment with ocrelizumab in PPMS	- Discuss the benefits and risks of DMTs in patients with CIS and two or more brain lesions - Offer DMTs to patients with active relapsing MS. - Prescribe alemtuzumab, fingolimod or natalizumab for highly-active MS - Offer ocrelizumab to ambulatory patients with PPMS	- Discuss the benefits of interferon-β or glatiramer acetate in CIS patients at high-risk of MS based on MRI features - Offer moderate-efficacy DMTs (30-50% decrease in relapse rates) (interferon-β, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod) to patients with active relapsing MS - Offer high-efficacy DMTs (>50% decrease in relapse rates) (natalizumab, alemtuzumab) to patients with more active relapsing MS
Switching DMTs	- Offer a more efficacious drug to patients treated with Interferon-β or glatiramer acetate who have ongoing disease activity	- Discuss switching DMTs in patients with one or more relapses and/or two or more new MRI lesions - Discuss switching DMTs in patients with side-effects or persistent laboratory test abnormalities - Discuss switching DMTs in patients treated with natalizumab who are JCV positive	- Consider switching DMTs in patients with ongoing relapses, side-effects, and possibly MRI only disease activity
Stopping DMTs	- Consider continuing DMTs in stable patients	- Advocate that patients who are stable continue taking DMTs - Consider advising stopping DMTs in patients with secondary progressive MS who have inactive disease and non-ambulatory - Consider stopping DMTs prior to conception and during pregnancy unless the risk of MS disease activity outweighs the benefits	- Consider stopping DMTs in patients with inactive secondary progressive MS - Consider stopping DMTs prior to conception and during pregnancy

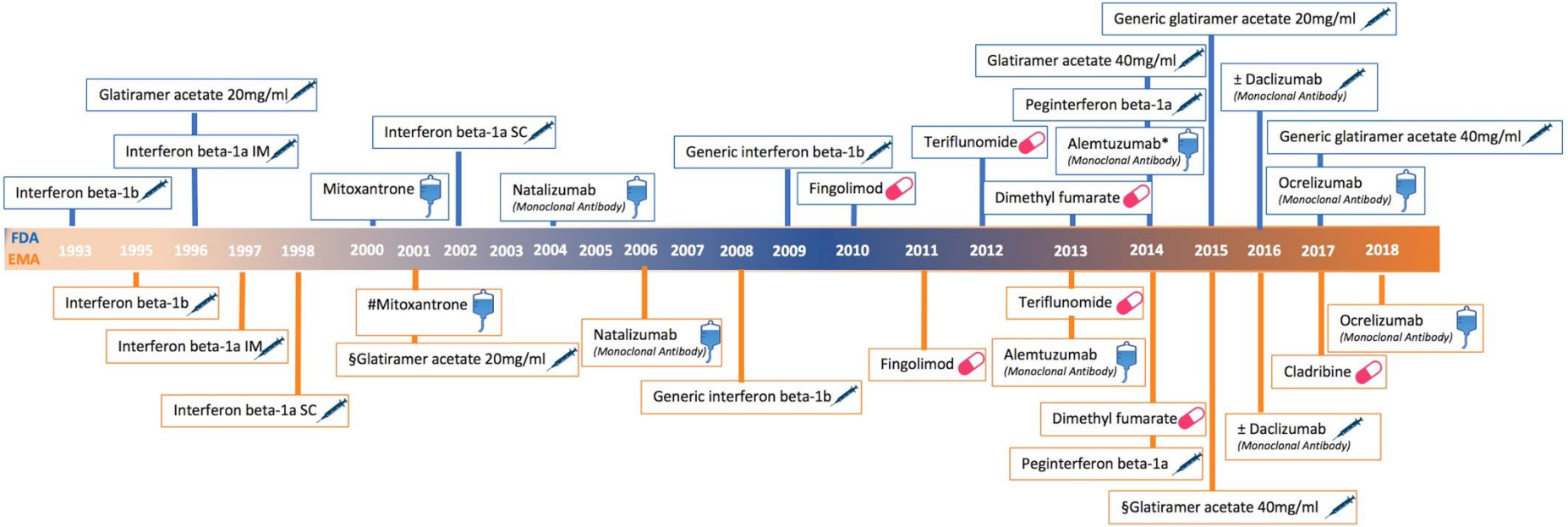
Abbreviations: ABN= Association of British Neurologists; AAN= American Academy of Neurology; CIS= clinically isolated syndrome. DMTs= disease-modifying therapies. EAN= European Academy of Neurology; ECTRIMS= European Committee for Treatment and Research in Multiple Sclerosis. JCV= John Cunningham virus. MS= multiple sclerosis. PPMS= primary progressive multiple sclerosis.

Table 1. Overview of licenced disease-modifying therapies for multiple sclerosis

DMT	*Evidence of efficacy from phase III pivotal RCTs*				DMT USE AND SAFETY MEASURES IN THE CLINICAL SETTING *BEFORE (baseline/screening) and AFTER (Follow-up) starting treatment*			
	Study Name	*Sample Size*	*Study Duration*	*Relapse Rate Reduction*	**Indication**	**Frequency of administration**	**Adverse Reactions**	**Treatment Monitoring**
Injectable (subcutaneous or intramuscular injection)								
Glatiramer acetate	*Copolymer-1 MS Study Group* [36]	*251*	*2 years*	*30% vs Placebo*	CIS RMS	Variable (three times a week, every day)	Injection-site reactions, immediate post-injection reaction	Baseline/screening: none Follow-up: none
Interferon-β preparations	*IFNB MS STUDY GROUP*[37] *PRISMS* [38]	*248* *560*	*3 years* *2 years*	*34% vs Placebo* *32% Vs Placebo*	CIS RMS	Variable (every other day, three times a week, once weekly, every 2 weeks)	Flu like illness, injection-site reactions, deranged LFTs, lymphopenia	Baseline/screening: FBC, LFTs Follow-up: FBC, LFTs
Oral								
Cladribine	*CLARITY* [39]	*870*	*96 weeks*	*58% vs Placebo*	RMS	Two courses of treatment over two years	Herpes zoster infections, lymphopenia, rash, alopecia	Baseline/screening: FBC, TB, HBV, HIV, MRI Follow-up: FBC
Dimethyl fumarate	*DEFINE* [40] *CONFIRM* [41]	*818* *1417*	*96 weeks* *2 years*	*53% vs Placebo* *44% Vs Placebo*	RMS	Twice a day	Flushing, gastrointestinal upset, lymphopenia, PML (rare)	Baseline/screening: FBC, LFTs, UEC, MRI Follow-up: FBC with differential every 3 months, LFTs, UEC, MRI
Fingolimod	*FREEDOMS* [42] *FREEDOMS II* [43]	*843* *713*	*24 months* *24 months*	*55% vs Placebo* *48% Vs Placebo*	RMS	Once a day	First-dose bradycardia, macular oedema, herpes zoster, deranged LFTs, hypertension, basal cell carcinoma, PML (rare)	Baseline/screening: ECG, OCT, dermatologic review, FBC, LFTs, VZV (vaccination is needed if VZV-IgG are negative), BP. First-dose cardiac monitoring. Follow-up: FBC, LFTs, annual skin check, BP, OCT at 4 months, MRI
Teriflunomide	*TOWER* [44]	*758*	*Variable (Minimum 48 week)*	*36% vs Placebo*	CIS RMS	Once a day	Nausea, diarrhoea, hair thinning, hypertension, deranged LFTs, teratogenicity	Baseline/screening: FBC, LFTs TB, BP Follow-up: FBC and LFTs (every 2 weeks

	TEMSO[45]	*721*	*108 weeks*	*31% Vs Placebo*				for the first 6 months and every 8 weeks thereafter), BP
Intravenous								
Alemtuzumab	*CARE MS I* [46]	*563*	*2 years*	*54% vs Interferon-β*	RMS	Treatment given over 2 years: - Year 1: once a day, for 5 days; - Year 2: once a day, for 3 days.	Infusion reactions, infections – herpes, varicella, listeria, superficial fungal, autoimmunity – ITP, nephropathy, thyroid disorders leukopenia, lymphopenia	Baseline/screening: FBC, UEC, LFTs, TFTs, TB, HBV, VZV, urinalysis, MRI, cervical smear. Follow-up: FBC, UEC, TFTs, urinalysis, MRI
	CARE MS II [47]	*628*	*2 years*	*50% vs Interferon-β*				
Mitoxantrone	*Mitoxantrone in relapsing-remitting MS* [48]	*2 years*	*51*	*66% vs Placebo*	RMS	Cumulative dose: usually once every 3 months for 2 years	Cardiotoxicity, infection, myelosuppression, gastrointestinal disturbance, alopecia, leukaemia and other malignancies	Baseline/screening: FBC, ECG Follow-up: FBC, TTE
Natalizumab	*AFFIRM* [49]	*2 years*	*942*	*68% vs Placebo*	RMS	Once every 28 days	Infusion reaction, PML, gastrointestinal disturbance, acute retinal necrosis (rare)	Baseline/screening: FBC, LFTs, JCV antibody, MRI Follow-ups: FBC, LFTs, JCV antibody, MRI
Ocrelizumab	*OPERA I & OPERA II* [18]	*96 weeks*	*1656*	*55% Vs Interferon-β*	RMS PPMS	- Initial 2 doses: once two weeks apart; - Subsequent doses: every 6 months	Infusion reactions, herpes virus associated infections, other infections	Baseline/screening: FBC, HBV, VZV Follow-up: FBC

Abbreviations: ARR: annualized relapse rate; BP = blood pressure; CIS= clinically isolated syndrome; ECG = electrocardiogram; FBC = full blood count; HBV = hepatitis B virus; HIV= human immunodeficiency virus ; ITP = idiopathic thrombocytopenic purpura; JCV = John-Cunningham virus; LFTs = liver function tests; MRI = magnetic resonance imaging; NNT: number needed to treat; OCT = optical coherence tomography; PML = progressive multifocal leukoencephalopathy; PPMS= primary progressive multiple sclerosis; RMS= relapsing multiple sclerosis; TB = tuberculosis; TFTs = thyroid function tests; TTE = transthoracic echocardiogram; UEC = urea, electrolytes, creatinine; VZV = Varicella Zoster virus.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Glatiramer acetate 20mg/ml
Interferon beta-1a IM
Interferon beta-1a SC
Mitoxantrone
Natalizumab (Monoclonal Antibody)
Generic interferon beta-1b
Fingolimod
Teriflunomide
Alemtuzumab* (Monoclonal Antibody)
Dimethyl fumarate
Peginterferon beta-1a
Glatiramer acetate 40mg/ml
Generic glatiramer acetate 20mg/ml
± Daclizumab (Monoclonal Antibody)
Generic glatiramer acetate 40mg/ml
Ocrelizumab (Monoclonal Antibody)
Interferon beta-1b
Interferon beta-1a IM
Interferon beta-1a SC
#Mitoxantrone
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Alemtuzumab (Monoclonal Antibody)
Dimethyl fumarate
Peginterferon beta-1a
§Glatiramer acetate 40mg/ml
Ocrelizumab (Monoclonal Antibody)
Cladribine
± Daclizumab (Monoclonal Antibody)

Figure 1

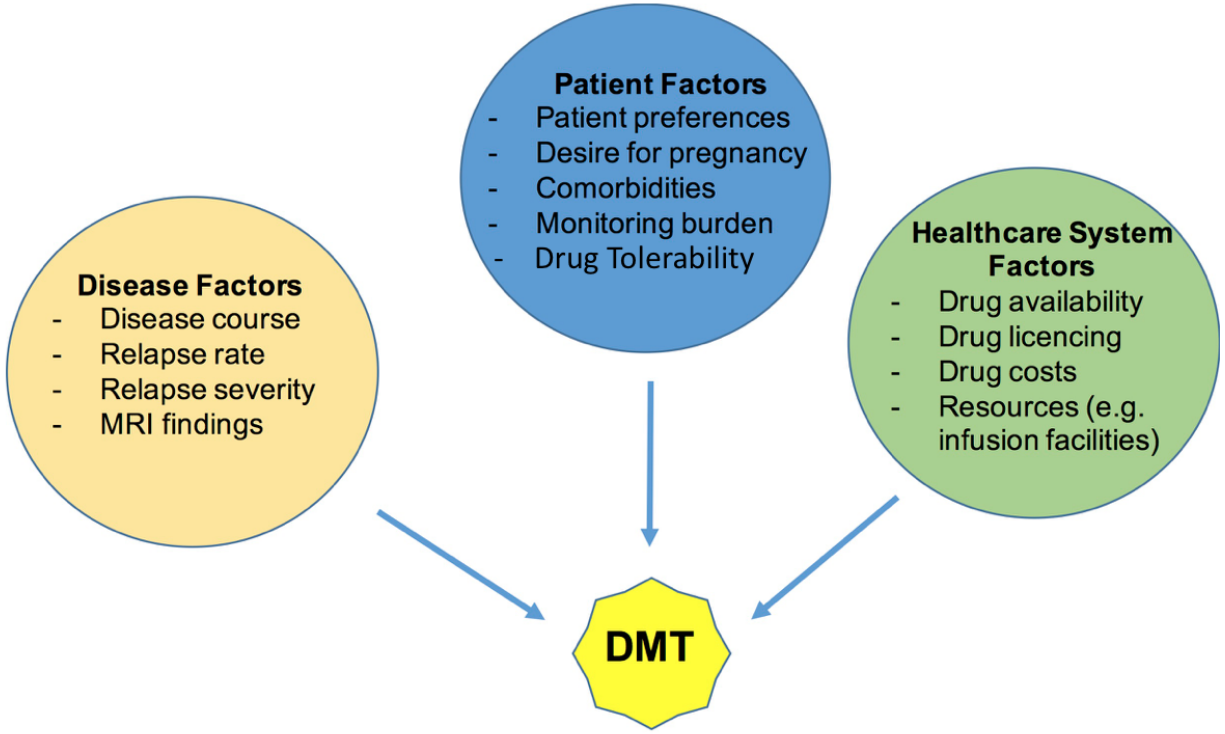
Patient Factors
- Patient preferences
- Desire for pregnancy
- Comorbidities
- Monitoring burden
- Drug Tolerability
Disease Factors
- Disease course
- Relapse rate
- Relapse severity
- MRI findings
Healthcare System Factors
- Drug availability
- Drug licencing
- Drug costs
- Resources (e.g. infusion facilities)
DMT

Figure 2