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Figure 1. Trajectory of MS

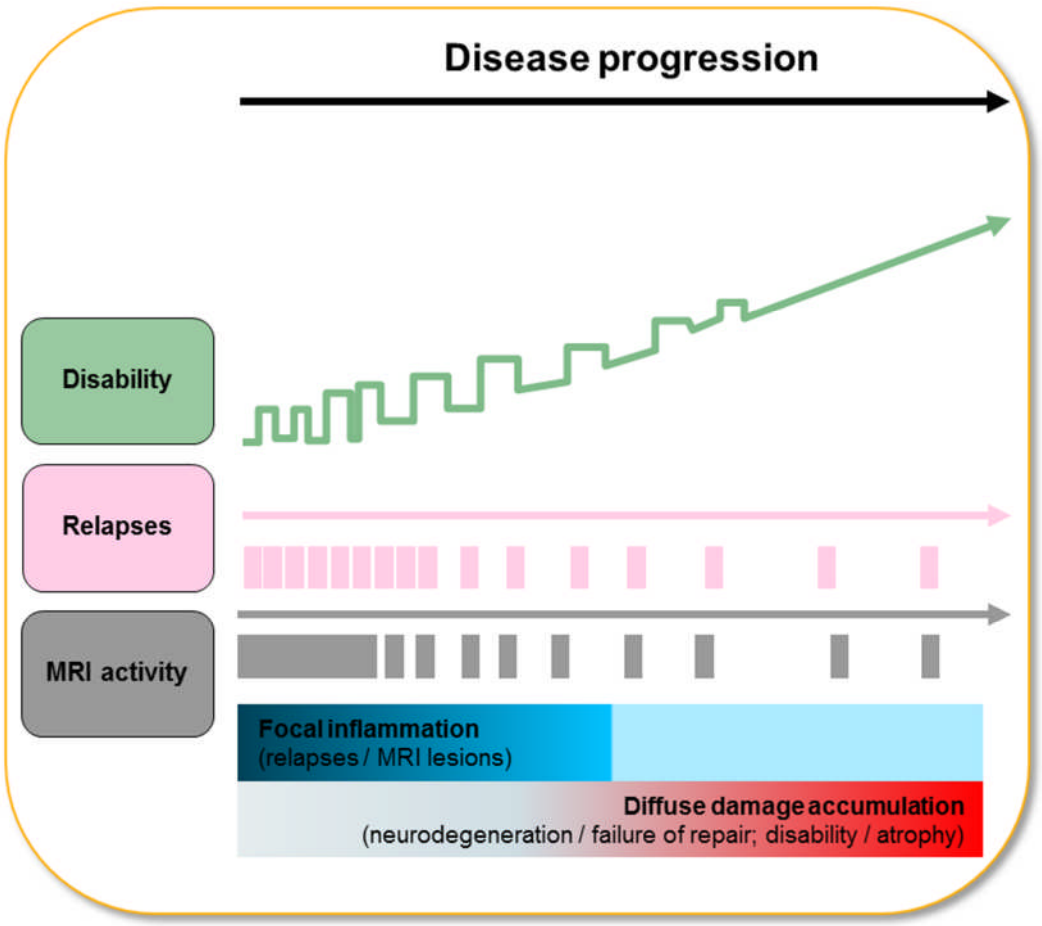

Figure1. Relapse onset MS leads to the progressive accumulation of disability after 10-15 years with fewer relapses and MRI T2 lesions or gadolinium-enhancing lesions.

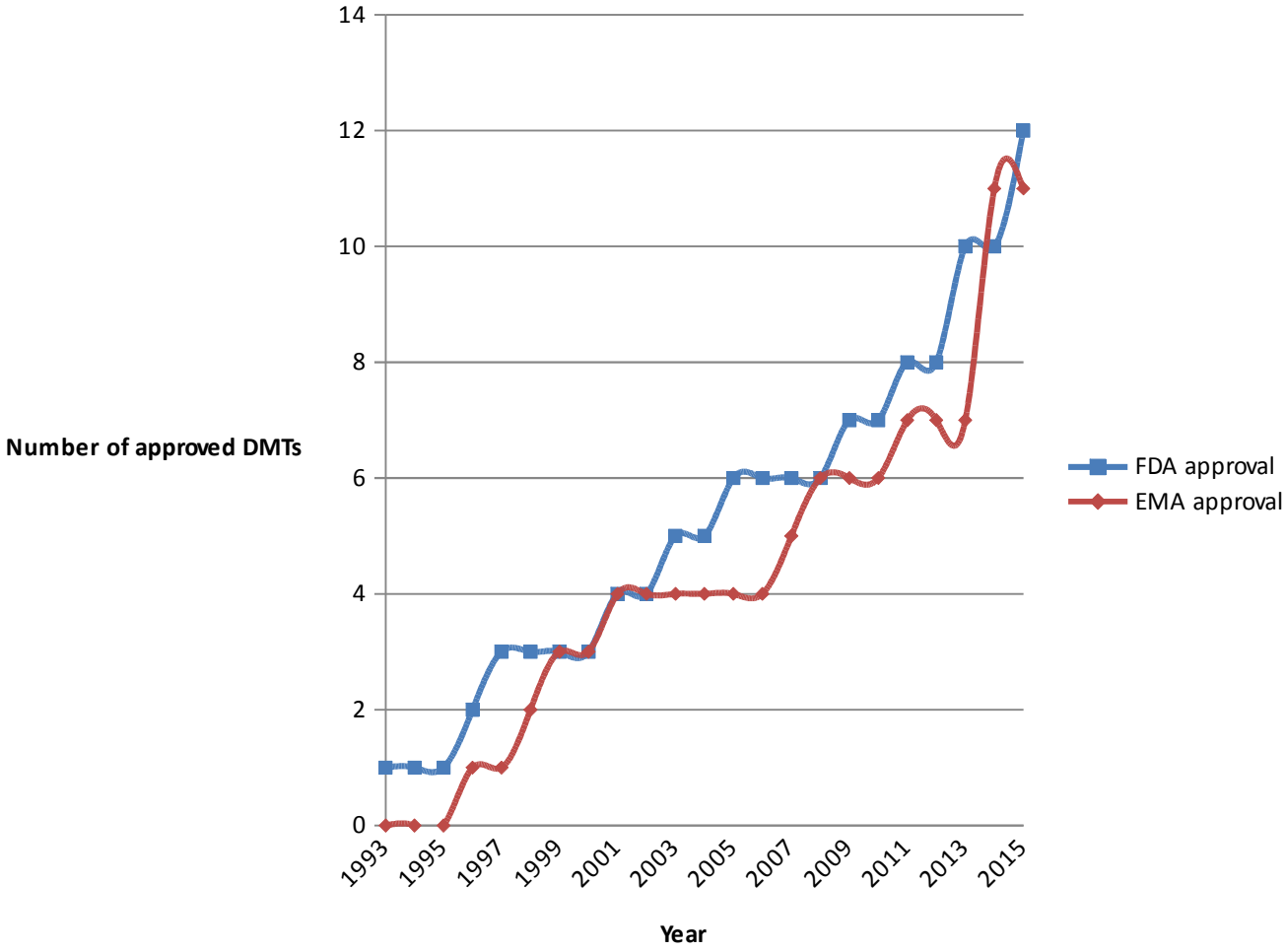

Figure 2. Armamentarium of disease-modifying therapies (DMTs) 2016

Approved DMTs in 2016; β-interferon-1a(Avonex), β-interferon-1b(betaferon), Glatiramer Acetate (Copaxone), Mitoxantrone (Novantrone)*, β-interferon-1a(Rebif), Natalizumab (Tysabri), Teriflunomide (Aubagio), Alemtuzumab (Lemtrada), Fingolimod (Gilenya), Dimethyl fumarate (Tecfidera),Interferon beta 1b (Extavia), β-interferon-1a (Plegridy).

This is a line graph of MS disease-modifying therapies (DMTs) which have European Medicines Agency (EMA) or Food and Drug Administration (FDA) approval. The vertical axis is the number of approved disease modifying therapies. The horizontal axis is year of approval. *Mitoxantrone (Novantrone) has FDA approval only.

Treatment	Mode and frequency	Side effects	Indication*	Notes
Interferon beta 1a (Avonex)	Intramuscular injection. 30 micrograms. once weekly.	>1:100; Flu-like, injection site reactions, headache, lymphopaenia, insomnia, diarrhoea, nausea and vomiting, depression, hair loss, liver function derangement, thyroid disease. *Caution re: neutralising antibodies in up to 46% of patients. Monitor antibody titres.	First-line: active RRMS with ≥2 relapses, or 1 relapse and new MRI lesions as per Mcdonald 2010 criteria in≤2 years. EDSS<6.5 (able to walk 20m) CIS and high risk of developing MS with MRI T2 lesions. *SPMS with ≥2 relapses in ≤2 years and EDSS progression ≤2 points over 2 years.	Fridge storage. Caution if depression/suicidal ideation.
Pegylated Interferon beta 1a (Plegridy)	Subcutaneous injection. Start with a dose of 63 micrograms on day 1, followed by 94 micrograms on day 15, then 125 micrograms on day 29 and once every 2 weeks thereafter.			Fridge storage. Keep out of sunlight.
Interferon beta 1a (Rebif)	Subcutaneous injection. Start at 22 micrograms three times weekly and escalate over 4 weeks to 44micrograms three times weekly.			Fridge storage
***Interferon beta 1b (Betaferon)**	Subcutaneous injection. Alternate days. Escalate to 250 micrograms over 3-6 weeks.			
***Interferon beta 1b (Extavia)**				
Glatiramer acetate (Copaxone)	Subcutaneous injection. 20 milligrams once daily. OR, 40 milligrams three times per week.	>1:100; injection site reactions including lipoatrophy, headache, depression, anxiety, nausea. Also IPIR with flushing, palpitations, dyspnoea, chest pain lasting 15-30 minutes.	First-line: active RRMS with ≥2 relapses, or 1 relapse and new MRI lesions as per Mcdonald 2010 criteria in ≤2 years. Able to walk more than 100m without aids. CIS and high risk of developing MS with MRI T2 lesions. SPMS with ≥2 relapses in ≤2 years and EDSS progression ≤2 points over 2 years.	If IPIR lasts longer than 30 minutes then patients should seek urgent medical attention.
Teriflunamide (Aubagio)	Oral. 7 or 14 milligrams once daily.	>1:100; liver function derangement, diarrhoea, nausea, hair thinning and loss.	First-line: active RRMS with ≥2 relapses, or 1 relapse and new MRI lesions in ≤2 years.	
Dimethyl fumarate (Tecfidera)	Oral. Initially 120 milligrams twice daily, and then increase after 7 days to 240mg twice daily.	>1:100; flushing, gastrointestinal upset, lymphopaenia, rash, ketonuria, proteinuria, liver function derangement. Very	First-line: active RRMS with ≥2 relapses, or 1 relapse and new MRI lesions in ≤2 years.	Taking oral doses with food may reduce the incidence of flushing and gastrointestinal effects.

		rare cases of PML reported	.	
Fingolimod (Gilenya)	Oral. 500 micrograms once daily.	>1:100; cough, headache, back pain, diarrhoea, infections, liver function derangement, lymphopaenia. <1:100; macular oedema. Very rare cases of PML reported.	Second-line: Highly active RRMS only with same/increased relapses despite treatment with beta interferon(pre-NICE approval) or glatiramer acetate (2014 post-NICE approval) over the last year. RRMS on Natalizumab at high risk of PML.(2014 post-NICE approval) First-line: Across UK, ABN guidance suggests fingolimod can be used if highly active RRMS.	Note: Bradycardia and atrioventricular conduction slowing can occur whilst taking the first dose of fingolimod, therefore the first dose is taken under medical supervision and cardiac monitoring for 6 hours.
Natalizumab (Tysabri)	Intravenous infusion. 300 milligrams once every 4 weeks.	>1:100; headache, dizziness, pruritic rash, infections. Clear risk gradient of PML.	First-line: RES RRMS with ≥2 relapses ≤ 1 year + no previous DMT and either a) ≥1 gadolinium enhancing MRI lesion or b) ≥9 T2-hyperintense MRI brain lesions if MRI available. Second-line: RES RRMS with ≥1 relapses ≤ 1 year + previous beta interferon not meeting stopping criteria and either a) ≥1 gadolinium enhancing MRI lesion or b) ≥9 T2-hyperintense MRI brain lesions if MRI available.	.
Alemtuzumab (Lemtrada)	Intravenous infusion. Initially: 12 milligrams daily for 5 consecutive days to a total dose of	>1:100; acute cytokine release syndrome (headaches, rash, fever, nausea,	First-line: active RRMS with ≥2 relapses in ≤2 years, or 1	Usually due to side effect profile, alemtuzumab is usually restricted to

	60 milligrams. Second course: 12 months post initial dose. 12 milligrams daily for 3 consecutive days to a total dose of 36 milligrams.	diarrhoea, hypotension), infections including herpes virus, endocrinopathy.	relapse and new MRI lesions. Second-line: Highly active RRMS on DMT and relapse within the last year and new MRI lesions..	those with more active RRMS. Pre-medications: oral or intravenous corticosteroid, oral antihistamine, and analgesic to prevent cytokine release syndrome. Oral prophylaxis with aciclovir for herpes infection and continued for one month.

Table 3. UK-licensed disease-modifying treatments (DMTs) for Relapsing Remitting MS

Glossary: RRMS (Relapsing Remitting Multiple Sclerosis), EDSS (Expanded Disability Status Scale), CIS (Clinically Isolated Syndrome), SPMS (Secondary Progressive Multiple Sclerosis), IPIR (immediate post-injection reaction), RES (Rapidly evolving severe), PML (Progressive Multifocal Leucoencephalopathy), ABN(Association of British Neurologists).

Comment: NHS England has taken on commisioning of the drugs since 2013 and advices that patients must be under the care of a designated MS centre which is registered to take part in the national risk sharing scheme involving the three beta interferon products and glatiramer acetate. The Association of British Neurologists (ABN) advices an annual review whilst on DMTs that will need to be conducted by the MS specialist neurologist who is also best placed to determine whether MRI scanning is required.

Sources:

1. Scolding N, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Practical Neurology 2015;15(4):273-279.

2. Multiple Sclerosis Trust. Disease Modifying Drugs. Multiple Sclerosis Trust Publication ID 90. November 2015.

3. National Institute for Clinical Excellence (NICE) Clinical Guidelines CG186. Multiple sclerosis in adults: management. October 2014.

4. National Health Service (NHS) England. Clinical commissioning policy: disease modifying therapies for patients with multiple sclerosis (MS) May 2014 NHS England/ D04/P/b

5. https://www.medicinescomplete.com/mc/martindale

	Drug	Interventional	Multi-disciplinary input
Fatigue	**Amantadine**		**Occupational therapy and physiotherapy: fatigue management assessment and exercise programme**
Cognition/ low mood	**Depression: citalopram, duloxetine**		**Neuropsychology service, cognitive behavioural therapy, occupational therapy**
Spasticity	**Baclofen, gabapentin, tizanidine, clonazepam, dantrolene**	**Intrathecal baclofen, botulinum toxin**	**Physiotherapy**
Bladder	**Frequency/urgency: Oxybutynin, solifenacin, tolterodine, mirabegron Nocturia: Desmopressin/ DDAVP spray**	**Residual bladder volume > 100mls: intermittent self-catheterisation or permanent catheter; intravesicular botulinum toxin,**	**Uro-neurology**
Sexual dysfunction	**Sildenafil, tadalafil, alprostadil, yohimbine**		**Uro-neurology**
Constipation	**Fibre/fluid, bulking agents, osmotic stimulant laxatives, suppositories, transanal irrigation**		
Faecal incontinence	**Codeine, loperamide**		**Biofeedback, neuro-gastroenterology**
Pain	**Amitriptyline, pregabalin, gabapentin, lamotrigine**		
Ataxia/Tremor	**Propranolol, clonazepam, levetiracetam, isoniazid (with pyridoxine), carbamazepine, ondansetron**	**Botulinum toxin, thalamotomy**	**Physiotherapy , occupational therapy, audiovestibular therapy**
Oscillopsia	**Gabapentin, memantine, levetiracetam, clonazepam, baclofen**		**Neuro-ophthalmology**

Table 4. Suggested symptomatic treatments in MS