				39%	
IFN β-1b (Betaseron)[50]	Not fully known	CIS and RMS (1st line)	SC injection, every other day	Relative reduction in ARR compared with placebo: 31%	Lymphopenia, flu-like symptoms, and injection-site reactions

ARR, annualized relapse rate; CDP, confirmed disability progression; CIS, clinically isolated syndrome; IFN β-1a, interferon beta 1a; IM, intramuscular; IV, intravenous; mAb, monoclonal antibody; PPMS, primary progressive multiple sclerosis; RMS, relapsing forms of multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis.

Treatment of Multiple Sclerosis: A Review

Supplementary Appendix

ADVANCES IN TREATMENT

Treating Acute Attacks

The terms 'acute attack', 'acute exacerbations' and 'relapses' are used interchangeably and refer to the onset or worsening of neurologic deficits lasting ≥24 hours in the absence of fever or infection.[1] When acute deterioration results from an increase in ambient temperature, fever or infection, this is considered a "pseudo exacerbation".[1] Glucocorticoids are used as first-line treatment for attacks as they provide short-term clinical benefit by reducing the severity and shortening the duration of attacks. Typically intravenous (IV) methylprednisolone 1 g/day for 3–5 days is given, often followed by an oral course of prednisone beginning at a dose of 60–80 mg/day and then tapered over 2 weeks.[1] Other glucocorticoid considerations are dexamethasone[1] and high-dose oral prednisone (in equivalent doses to high-dose IV methylprednisolone) that appears to be equally effective.[2]

Second-line treatment for patients resistant or refractory to glucocorticoid treatment includes plasmapheresis, IV immunoglobulin (IVIG), and adrenocorticotropic hormone (ACTH). The use of plasmapheresis (plasma exchange) is reserved for cases of severe symptoms refractory to glucocorticoids and generally involves five to seven exchanges (40–60 mL/kg per exchange) every other day for 14 days.[1] IVIG is not approved in this indication but is sometimes used off-label in steroid-unresponsive patients as second- or third-line treatment; notably, this is the preferred treatment for postpartum patients. ACTH is another FDA-approved option but is rarely used because of high cost and uncertain advantages over glucocorticoids; in individuals

with poor intravenous access or who are unable to tolerate oral corticosteroids, ACTH is given intramuscularly at 80-120 units for two to three weeks and can be tapered.

Symptomatic Therapies

For all patients, it is useful to encourage attention to a healthy lifestyle, including maintaining an optimistic outlook, a healthy diet, and regular exercise as tolerated (swimming is often well-tolerated because of the cooling effect of cold water in heat-sensitive individuals). Because vitamin D deficiency is considered a risk factor for MS and osteopenia, it is reasonable also to correct with oral vitamin D. Supplementary Table 1 summarizes treatment options for common symptoms in MS.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Symptomatic Treatment Approaches in Multiple Sclerosis (MS)

MS Symptom	Approximate Frequency in MS	Non-Pharmacological Treatments: Key Recommendations	Pharmacological Treatments: Key Recommendations
Spasticity and spasms[3-5]	90%	• Physiotherapy (including stretching) • Occupational therapy	• Baclofen (oral *[10–120 mg/day]* and intrathecal) • Tizanidine *(2–36 mg/day)* • Gabapentin *(300–3600 mg/day)* • Clonazepam *(0.25–2 mg/day)* • Diazepam *(6-15 mg/day)* • Cannabinoids • Botulinum toxin injection
Impaired gait[6-8]	80%	• Adaptive devices • Physiotherapy • Functional electrical stimulation	• 4-Aminopyridine (Dalfampridine) (*20mg/day)*
Pain[4,5]	Up to 86%	• Pain Management	• Gabapentin *(300–2400 mg/day)* • Pregabalin *(150–600 mg/day)* • Duloxetine (20-120 mg/day) • Amitriptyline *(25–150 mg/day)* • Carbamazepine *(100–1600 mg/day)* • Lamotrigine *(200–400 mg/day)* • Topiramate *(200–300 mg/day)*
Ataxia/tremor[4,5,9]	80%	• Physiotherapy • Occupational therapy • Wrist weights • Thalamotomy • Deep-brain stimulation	• Carbamazepine *(400–600 mg/day)* • Propranolol *(40–240 mg/day)* • Topiramate *(100–333 mg/day)*

			• Cannabinoids • Primidone *(up to 750 mg/day)* • Ondansetron *(8 mg/day)* • Clonazepam *(3–6 mg/day)* • (These agents have been tried with mixed success; response is generally poor)
Bladder dysfunction[4,5]	70–80%	Assessments: • Urodynamic testing Treatments: • Pelvic floor exercises • Electrical stimulation • Fluid intake management • Urinary aids	• Mirabegron • Oxybutynin • Tolterodine • Solifenacin • Trospium chloride *(40–60 mg/day)* • Desmopressin *(up to 20 µg)*
Depression[4,5]	50%	• Psychotherapy • Counselling	• Fluoxetine • Sertraline • Escitalopram • Bupropion • Venlafaxine
Fatigue[4,5]	75%	• Cooling • Regular exercise • Physiotherapy • Sleep hygiene	• Modafinil *(200–400 mg/day)* • Armodafinil • Methylphenidate
Cognitive dysfunction[4,5]	40–70%	• Attention training • Memory training • Cognitive rehabilitation	• Lisdexamfetamine
Paroxysmal symptoms[4,5]	10–20%	• Thermocoagulation • Radiotherapy	• Carbamazepine *(100–300 mg/day)* • Oxcarbazepine • Lamotrigine *(up to 400 mg/day)* • Gabapentin *(up to 1600 mg/day)* • Topiramate *(up to 300 mg/day)*