Chapter 74: Multiple Sclerosis

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 56, Multiple Sclerosis.

KEY CONCEPTS

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1. Multiple sclerosis (MS) etiology is unknown, but it appears to be autoimmune in nature. Currently, there is no cure.

2. Multiple sclerosis is characterized by central nervous system (CNS) demyelination and axonal damage.

3. Multiple sclerosis is classified into several categories, differentiated by disease progression over time, clinical presentation, and response to therapy.

4. Studies only support one Food and Drug Administration (FDA)-approved disease-modifying therapy (DMT), ocrelizumab (Ocrevus), in patients with progressive forms of the illness. However, information derived from multiple studies suggests younger patients with progressive disease and those with either superimposed acute relapses or enhancing lesions on magnetic resonance imaging (MRI) scans may benefit from some of the presently used DMTs.

5. MS diagnosis is made primarily based on clinical symptoms and examination but does require evidence of dissemination of lesions over time in multiple parts of the CNS and/or optic nerve. Additional diagnostic criteria include use of MRI, spinal fluid evaluation, and evoked potentials to aid in the diagnosis.

6. Exacerbations or relapses of MS can be disabling and are treated with high-dose glucocorticoids, such as intravenous (IV) methylprednisolone. The onset of clinical response is typically within 3 to 5 days.

7. Treatment of relapsing-remitting multiple sclerosis (RRMS) with the DMTs interferon-β (IFN-β) (Avonex, Betaseron, Rebif, Extavia), glatiramer acetate (Copaxone), natalizumab (Tysabri), ocrelizumab (Ocrevus), mitoxantrone (Novantrone), fingolimod (Gilenya), siponimod (Mayzent), ozanimod (Zeposia), ponesimod (Ponvory), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), diroximel fumarate (Vumerity), monomethyl fumarate (Bafiertam), cladribine (Mavenclad), Ofatumumab (Kesimpta), and alemtuzumab (Lemtrada) can reduce the annual relapse rate, lessen relapse severity, slow progression of MRI changes, and slow progression of disability and cognitive decline. In addition, DMTs have been shown to reduce the likelihood of developing a second attack after a first clinically isolated syndrome (CIS) consistent with MS.

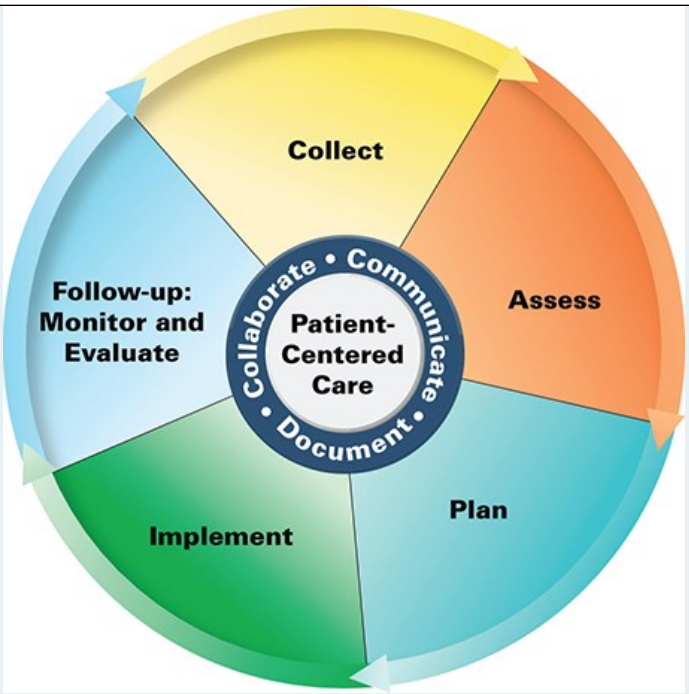
8. In most cases, treatment with DMTs should begin promptly after the diagnosis of RRMS or after a CIS if the brain MRI suggests a high risk of further attacks. Natalizumab, and other choices associated with problematic adverse events, should be reserved for those patients who have failed one or more standard therapies and those with poor prognostic signs.

9. The definition of “treatment inadequacy” for RRMS remains unclear, and therapy changes after “treatment failure” should be individualized.

10. Patients suffering with MS frequently have spasticity, bladder dysfunction, fatigue, neuropathic pain, cognitive dysfunction, and depressive symptoms that may require treatment. Providers must counsel patients that DMTs will not relieve these symptoms and that depression is common and can pose the risk of suicide.

PATIENT CARE PROCESS

Patient Care Process for Multiple Sclerosis



Collect

- Patient-specific demographics such as age, race, gender, geographical places of residence before or after the age of 15, current smoking level and history, family history of MS, and previous infection with certain viruses
- Laboratory values such as vitamin D, liver function tests, complete metabolic panel, and complete blood count (CBC)
- Magnetic resonance imaging (MRI) of the brain and spinal cord with and without contrast
- Lumbar puncture for oligoclonal bands
- Visual-evoked potential results
- Optical coherence tomography (OCT)
- Current diagnosis and date of initial diagnosis and current and past medications

Assess

- Clinical classification of MS (RRMS, SPMS, or PPMS)
- Disease progression using the Expanded Disability Status Scale (EDSS), and MRI results
- Total number of disease exacerbations or relapses
- Duration of therapy and dose for current and past medications, adverse medication reactions experienced during treatment, and medication adherence

Plan*

- Choose a therapy that has the best risk versus benefit profile for use in the specific form of MS diagnosed, as well as patient-specific characterizations and previous treatment history (Tables 74-1 to 74-3)
- Choose a therapy with the best adherence profile (twice yearly infusion vs three times weekly injectable), and more tolerable adverse

medication reactions based on stratified risk factors (JC virus)

- Create a patient-specific monitoring plan based on the therapy chosen (Table 74-2)
- Identify the presence of secondary symptoms requiring pharmacologic management (Table 74-4)

Implement*

- Start primary MS therapy as soon as possible to decrease the chance for disease progression during treatment changes
- Figure 74-3 represents a potential algorithm for MS treatment
- Add pharmacologic treatment for secondary symptoms when appropriate
- Discuss with patients the role of complementary and alternative therapies (Table 74-5)

Follow-up: Monitor and Evaluate

- Safety of current DMT at each visit to ensure the current treatment is best for the specific patient
- Monitor for common adverse medication reactions with each specific DMT (Table 74-2) or any adverse medication reactions that are new once therapy is initiated or changed
- Treatment response (reduction in primary, secondary, and tertiary symptoms of MS) or the occurrence of exacerbations and relapses
- Yearly change in brain lesions via MRI
- Change in daily functioning using the EDSS and other clinical factors used to predict MS prognosis (Table 74-6)

**Collaborate with patients, caregivers, and other healthcare professionals.*

TABLE 74-1

Disease-Modifying Therapy

Medication	Brand Name	Indication	Initial Dose	Usual Dose	Comment
First-generation agents					
Self-injectables					
Interferon-β_{1a}	Avonex	Relapsing forms of MS	30 mcg (6 million IU) IM once weekly	30 mcg IM once weekly	Considered low potency interferon
	Rebif	Relapsing forms of MS	22 mcg SQ three times a week	22 or 44 mcg SQ three times a week	Considered a high potency interferon
Interferon-β_{1b}	Betaseron, Extavia	Relapsing forms of MS	250 mcg (8 million IU) SQ every other day	250 mcg SQ every other day	Betaseron/Extavia is considered a high potency interferon. Pregnancy category C

Pegylated Interferon-β_{1a}	Plegridy	RRMS	6.3 mcg SQ day 1, then 94 mcg SQ on day 15, then 125 mcg SQ on day 29, then 125 mcg SQ every 14 days	125 mg SQ every 14 days	Can pre-medicate or concurrently use an antipyretic/analgesic for flu-like symptoms. Pregnancy category C
Glatiramer acetate	Copaxone, Glatopa	CIS, RRMS	20 mg SQ once daily or 40 mg SQ three times a week	20 mg SQ once daily or 40 mg SQ three times a week	Glatopa is the generic version of Copaxone. Pregnancy category B
IV infusion					
Mitoxantrone	Novantrone	SPMS and worsening RRMS	12 mg/m^2 IV every 3 months	12 mg/m^2 IV every 3 months	Lifetime dose should not exceed 140 mg/m^2. Pregnancy category D
Second-generation agents					
Oral					
Fingolimod	Gilenya	Relapsing forms of MS, in patients 10 years and older	Adult: 0.5 mg orally once daily. Pediatric: <40 kg 0.25 mg orally once daily, >40 kg 0.5 mg orally once daily	Adult: 0.5 mg orally once daily. Pediatric: <40 kg 0.25 mg orally once daily, >40 kg 0.5 mg orally once daily	Medication Guide required. Pregnancy category C
Siponimod	Mayzent	Relapsing forms of MS	CYP2C9 *1/*1, *1/*2, *2/*2: 0.25 mg once daily on days 1 and 2, then 0.5 mg once daily on day 3, then 0.75 mg once daily on day 4, then 1.25 mg once daily on day 5. CYP2C9 *1/*3, *2/*3: 0.25 mg once daily on days 1 and 2, then 0.5 mg once daily on day 3, then 0.75 mg once daily on day 4	CYP2C9 *1/*1, *1/*2, *2/*2: 2 mg once daily beginning on day 6. CYP2C9 *1/*3, *2/*3: 1 mg once daily beginning on day 5	Medication Guide required. May cause fetal harm. CYP2C9 genotype testing required prior to initiating dose
Ozanimod	Zeposia	Relapsing forms of MS	0.23 mg once daily on days 1-4, then 0.46 mg once daily on days 5-7	0.92 mg once daily beginning on day 8	Medication Guide required. May cause fetal harm
Ponesimod	Ponvory	Relapsing forms of MS	2 mg on days 1 and 2, 3 mg on days 3 and 4, 4 mg on days 5 and 6, 5 mg on day 7, 6 mg on day 8, 7 mg on day 9, 8 mg on day 10, 9 mg on day 11, 10 mg on days 12-14	20 mg on day 15 and thereafter	Medication Guide required. May cause fetal harm
Dimethyl fumarate	Tecfidera	Relapsing forms of MS	120 mg delayed release twice daily for 7 days	240 mg delayed release twice daily	Pregnancy category C
Diroximel fumarate	Vumerity	Relapsing forms of	231 mg twice daily for 7 days	462 mg twice daily	May cause fetal harm based on animal data

		MS			
Monomethyl fumarate	Bafiertam	Relapsing forms of MS	95 mg twice daily for 7 days	190 mg twice daily	May cause fetal harm based on animal data
Teriflunomide	Aubagio	Relapsing forms of MS	7 mg orally once daily	7 or 14 mg orally once daily	Cholestyramine and charcoal accelerate teriflunomide elimination. Pregnancy category X
Cladribine	Mavenclad	RRMS and active SPMS	3.5 mg/kg over 2-year treatment course, administered as 1.75 mg/kg in each year. Divide the 1.75 mg/kg dose over 2 cycles, each cycle lasting 4 to 5 consecutive days; do not administer more than 20 mg/day. In the first-year treatment course, initiate the first cycle at any time; administer the second cycle 23 to 27 days after the last dose of the first cycle	Second-year treatment course: Initiate the first cycle ≥43 weeks after the last dose of the first year's second cycle. Administer the second cycle 23 to 27 days after the last dose of the second year's first cycle. Following 2 years of treatment, do not administer oral cladribine during the next 2 years	Medication Guide required Contraindicated for use in females and males of reproductive potential. Lymphocytes must be within normal limits before initiating first treatment course and >800 cells/mm^3 (0.8 x10^9/L) before the second treatment course
IV infusion					
Natalizumab	Tysabri	Relapsing forms of MS	300 mg IV every 4 weeks	300 mg IV every 4 weeks	REMS Program required. Pregnancy category C
Alemtuzumab	Lemtrada	RRMS	First treatment course: 12 mg/day IV for 5 consecutive days (60 mg total dose)	Second treatment course: 12 mg/day IV for 3 consecutive days (36 mg total dose) administered 12 months after first treatment course	REMS Program required. Pregnancy category C. May pre-medicate with 1,000 mg methylprednisolone (or equivalent) immediately prior to infusion for first 3 days. Also, administer herpes viral prophylaxis starting on first day of treatment and continued for at least 2 months after completion of treatment or until $CD4^+$ count is at least 200 cells/mm^3 (0.2 × 10^9/L), whichever occurs last
Ocrelizumab	Ocrevus	Relapsing forms of MS and PPMS	First treatment course: 300 mg IV followed by 300 mg IV 2 weeks later. Start infusion at 30 mL/hr, then increase by 30 mL/hr every 30 minutes as tolerated to a maximum of 180 mL/hr for a duration of 2.5 hours or longer	Maintenance treatment (given 6 months after the end of first treatment, and every 6 months thereafter): 600 mg IV starting at 40 mL/hr and increased by 40 mL/hr every 30 minutes as tolerated to a maximum	REMS Program required. Fetal risk cannot be ruled out. Premedication: antihistamine 30 to 60 minutes prior to infusion and 100 mg methylprednisolone or equivalent corticosteroid 30 minutes prior to infusion. Can also consider and antipyretic. Observe patient for at

				rate of 200 mL/hr for a duration of 3.5 hours or longer	least 1 hour post infusion
Self-injectable					
Ofatumumab	Kesimpta	Relapsing forms of MS	20 mg once weekly for 3 doses (weeks 0, 1, 2)	20 mg once monthly starting at week 4	Medication Guide required. Single-dose prefilled syrine pen. Based on animal data, may cause fetal harm

CIS, clinically isolated syndrome; IM, intramuscular; PRMS, primary relapsing multiple sclerosis; REMS, Risk Evaluation and Mitigation Strategy; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SQ, subcutaneous; IU, international units.

Data from References 58 and 59.

TABLE 74-2

Adverse Medication Reactions and Monitoring Parameters

Medication	Adverse Medication Reaction	Monitoring Parameter	Comments
Interferon-β_{1a}	Depression, flu-like symptoms, leukopenia, injection site reactions	Electrolytes, CBC, LFTs, thyroid function, LVEF, depression LFTs at baseline, 1 month, and every 3 months for a year, and every 6 months thereafter	Avoid use in untreated severe depression
Interferon-β_{1b}	Depression, injection site reactions, leukopenia, flu-like symptoms	Electrolytes, CBC, LFTs, thyroid function, depression	Avoid use in untreated severe depression. More frequent injection site reactions reported
Glatiramer acetate	Injection site reactions, infection, hypersensitivity, chest tightness, urticaria	MRI, tissue necrosis, postinjection reaction	Chest tightness, urticaria can occur at any dose
Mitoxantrone	Bone marrow suppression, neutropenia, cardiotoxicity, AML, nausea, vomiting, diarrhea, alopecia	CBC, ECG, LVEF, LFTs	Secondary leukemia. Lifetime maximum dose due to cardiac toxicity
Fingolimod	Lymphocytopenia, macular retinal edema, AV block, infection, headache	CBC, ECG, varicella zoster antibody, blood pressure, ophthalmic examination, LFTs	Requires first dose observation. Contraindicated in patients receiving Class I and III antiarrhythmic medications and those with recent cardiac diseases*, second- and third-degree AV block. Ketoconazole increases serum concentrations (3A4 inhibition). Vaccine efficacy may be decreased
Siponimod	Infections, macular edema, bradyarrhythmia and atrioventricular conduction delays, decreased pulmonary function, liver injury, increased blood pressure	CBC, ECG, varicella zoster antibody, blood pressure, ophthalmic examination, LFTs	Requires CYP2C9 genomic testing. Contraindicated in *3/*3 genotype. Medication interactions with 2C9 and 3A4 inhibitors and inducers

Ozanimod	Infections (URTI), AV block, bradycardia, hepatotoxicity, increased blood pressure, lymphopenia, macular edema, neurotoxicity, PML, decreased pulmonary function, varicella zoster infections	CBC, ECG, varicella zoster antibody, blood pressure, ophthalmic examination, LFTs	Medication interactions with strong CYP2C8 inhibitors and inducers and BCRP inhibitors. Avoid use of live attenuated vaccines during and for up to 3 months after treatment
Ponesimod	Infections, bradyarrhythmia and atrioventricular conduction delays, pulmonary function, liver injury, increased blood pressure, cutaneous malignancies, macular edema	CBC, ECG, LFTs, ophthalmic examination, varicella zoster antibody	Contraindicated in patients with recent cardiac diseases*, second- and third-degree AV block, sick sinus syndrome, or sino-atrial block unless patient has functioning pacemaker. Four-hour observation monitoring for patients with certain preexisting cardiac conditions
Dimethyl fumarate	Flushing, rash, pruritus, GI discomfort, lymphocytopenia, increased LFTs, albuminuria, PML	CBC, LFTs, MRI	Taking with food decreases incidence of flushing
Diroximel fumarate	Flushing, GI upset, hepatotoxicity, infections, lymphopenia, PML	CBC, LFTs, MRI	Less GI adverse events compared to dimethyl fumarate and may be better tolerated
Monomethyl fumarate	Flushing, GI upset, hepatotoxicity, infections, lymphopenia, PML	CBC, LFTs, MRI	Less GI adverse events compared to dimethyl fumarate and may be better tolerated
Teriflunomide	Steven-Johnson syndrome, liver failure, neutropenia, respiratory infection, activation of TB, alopecia, neuropathy	CBD, LFTs, blood pressure, pregnancy, TB test	Contraindicated in severe hepatic impairment. Possibility of TB reactivation. Active metabolite of leflunomide
Cladribine	Bone marrow suppression, cardiotoxicity, hepatotoxicity, infection, malignancy, neurotoxicity, PML, renal toxicity, hypersensitivity, headache	CBC before starting, 2 and 6 months after the first course of each cycle and periodically. HIV, HBV, HCV, TB screening, VZV antibody, pregnancy test, LFTs, MRI, PML, infection	Contraindicated with current malignancy, HIV infection or active chronic infections, pregnancy and lactation
Natalizumab	PML, depression, fatigue, respiratory infection, arthralgia, hepatotoxicity	JCV antibody, infection, MRI, LFTs, hypersensitivity reactions,	Risk of PML. Risk of IRIS when discontinued due to PML
Alemtuzumab	Infusion reactions, infections (nasophyaryngitis, UTI, URI, herpes viral infections), autoimmune disorders, thyroid disorders, immune-mediated thrombocytopenic purpura, goodpasture syndrome	CBC, thyroid function, antibodies to varicella zoster virus, HPV screening, serum creatinine, TB prior to treatment, infusion reactions, skin exams, urinalysis	Contraindicated with HIV infection. Birth control should be used during treatment and for 4 months after each treatment course. Nursing is not recommended during treatment and for 4 months following each treatment course
Ocrelizumab	Infusion reactions, nasopharyngitis, upper respiratory tract infection, headache, urinary tract infection, herpes virus–related infections, neoplasms	MRI, active infection before infusion, infusion reactions during and after infusion, skin infections	Live vaccines are not recommended during treatment and after treatment until B-cell repletion, administer all live vaccines 6 weeks before treatment. Evaluate for hepatitis B infection before first dose. Avoid pregnancy during treatment and for 6 months after stopping

			treatment
Ofatumumab	Infections, injection site reactions, reduction in immunoglobulins, headache	HBV screen, serum immunoglobulins, CBC, PML, MRI	Contraindicated in active HBV infection. Immunize at least 4 weeks prior to initiation for live or live-attenuated vaccines and 2 weeks prior for inactivated vaccines

*Cardiac disease including myocardial infarction, unstable angina, stroke, transient ischemic attack, and heart failure NYHA Class III/IV.

AML, acute myeloid leukemia; CBC, complete blood count; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; IRIS, immune reconstitution inflammatory syndrome; PML, progressive multifocal leukoencephalopathy; LFT, liver function test.

TABLE 74-3

Key Recommendations on Treatment and Access Considerations

- Initiating therapy with an FDA-approved DMT is recommended as soon as possible following a definite diagnosis of relapsing MS. It can also be considered for selected patients with a first clinical attack consistent with MS where other potential causes have been excluded, as well as for patients with progressive MS with clinical relapses and/or inflammatory activity.
- Choice of initial or alternative DMT is complex and should be collaboratively done by the treating clinician and the patient.
- Clinicians should evaluate barriers to treatment adherence and counsel patients on its importance.
- Continue therapy indefinitely unless there is a clear lack of benefit, intolerable adverse medication reactions, inadequate patient adherence, new data that reveal other reasons for cessation, or a better therapy becomes available.
- The absence of relapses while on treatment should not justify treatment discontinuation. When switching DMTs due to suboptimal response, choose an agent with an alternative mechanism of action.
- For patients with highly active MS, clinicians should prescribe alemtuzumab, fingolimod, or natalizumab.
- Natalizumab can be initiated in patients with MS and positive anti-JCV antibody indexes above 0.9 only when there is a reasonable benefit outweighing the severe but low risk of PML.
- Ocrelizumab can be offered to patients with PPMS when the risks of treatment does not outweigh the benefits.
- Clinicians should counsel female patients to stop their DMT before conception for planned pregnancies. If accidental exposure occurs, clinicians should discontinue DMTs during pregnancy. They should not be initiated during pregnancy unless the risk of MS activity outweighs the DMT risk.
- Due to the significant variability in therapeutic response, contraindications, risk tolerance, and treatment adherence seen in the MS population, patient and clinician access to all available therapies is necessary as this may influence decisions regarding the route of administration and/or adverse medication effect tolerance.
- Patient access to medication should not be limited by the frequency of relapses, age or other personal characteristics, or level of disability. Therapy should not be withheld to allow for determination of coverage by payers, as this puts the patient at increased risk for recurrent disease activity.

Data from References 58 and 111.

TABLE 74-4

Treatment of Select Primary MS Symptoms

Spasticity	Bladder Symptoms	Sensory Symptoms	Fatigue
Baclofen Dantrolene Diazepam Clonazepam Tizanidine Tiagabine Gabapentin Pregabalin Botulinum toxin type A Dalfampridine	Propantheline Oxybutynin Dicyclomine DDAVP Self-catheterization Imipramine or amitriptyline Prazosin or terazosin Botulinum toxin type A Solifenacin Darifenacin Trospium Hyoscyamine Mirabegron Tamsulosin Tolerodine	Carbamazepine Phenytoin Amitriptyline or other TCAs Gabapentin Lamotrigine Pregabalin Duloxetine	Amantadine Antidepressants Modafinil Methylphenidate Dextroamphetamine Armodafinil Fluoxetine

DDAVP, desmopressin acetate; TCA, tricyclic antidepressant.

Data from References 28, 131, and 133-136.

TABLE 74-5

American Academy of Neurology Evidence-Based Recommendations on CAM Therapies in MS

CAM Therapy	Type of MS	Symptoms and Reported Use	Effective	Ineffective	Recommendation Level
Oral cannabis extract	RRMS, SPMS, PPMS, MSU	Symptoms of spasticity and pain	x		A
	RRMS, SPMS, PPMS	Signs of Spasticity (short term), tremor (short term)		x	B
	MSU	Signs and symptoms of spasticity (long term)	x		C
	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence			U
Synthetic THC	RRMS, SPMS, PPMS	Symptoms of spasticity, pain	x		B
	RRMS, SPMS, PPMS	Signs of spasticity (short term), tremor (short term)		x	B

	MSU	Signs and symptoms of spasticity (long term)	x		C
	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence, central neuropathic pain			U
Sativex oromucosal spray	MSU	Symptoms of spasticity, pain, urinary frequency	x		B
		Signs of spasticity, incontinence episodes		x	B
		Tremor		x	C
		Anxiety/sleep, cognition, QOL, fatigue			U
Smoked cannabis	RRMS, SPMS, MSU	Spasticity, pain, balance and posture, cognition			U
Ginkgo biloba	RRMS, SPMS, PPMS	Fatigue	x		C
		Cognitive function		x	A
Lofepramine plus phenylalanine with B_{12} (Cari Loder regimen)	RRMS, SPMS, PPMS	Disability, symptoms, depression, fatigue		x	C
Reflexology	MSU	Paresthesia	x		C
		Pain, HRGOL, disability, spasticity, fatigue, cognition, bowel/bladder function, depression, anxiety, insomnia			U
Bee venom	RRMS, SPMS	MRI lesion number and volume, relapses, disability, fatigue, HRQOL		x	C
Magnetic therapy	RRMS, SPMS, PPMS	Fatigue	x	x	B
		Depression			B
Low-fat diet with omega-3 supplementation	RRMS	Relapses, disability, MRI lesions, fatigue, QOL		x	B

CAM, complementary and alternative medicine; HRQOL, health-related QOL; MS, multiple sclerosis; MSU, MS type unspecified; PCE, oral cannabis extract; PPMS, primary progressive MS; QOL, quality of life; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; THC, tetrahydrocannabinol; A, established as effective or ineffective; B, probably effective or ineffective; C, possibly effective or ineffective; U, insufficient evidence to determine effectiveness or ineffectiveness.

Data from Reference 139.

TABLE 74-6

Prognostic Indicators in Multiple Sclerosis

Indicator	Favorable Prognosis	Unfavorable Prognosis
Age at onset	<40 years	>40 years
Gender	Female	Male
Initial symptoms	Optic neuritis or sensory symptoms	Motor or cerebellar symptoms; polysymptomatic
Disability	Late	Early
Attack frequency in early disease	Low	High
Course of disease	Relapsing/remitting	Progressive
Recovery after the first event	Good	Poor
T2 lesions	Low load	High load
T1 black hole lesions	Low rate	High rate
Growth of lesions	Slow	Rapid
Locations of lesions	Single	Multiple

Data from References 45 and 46.

BEYOND THE BOOK

BEYOND THE BOOK

Create a table that lists the current FDA-approved multiple sclerosis (MS) therapies for relapsing-remitting MS (RRMS), primary progressive MS (PPMS), clinically isolated syndrome (CIS), and secondary progressive MS (SPMS). Include the mechanism of action (MOA) and how you believe this helps reduce MS symptoms. This activity will get you familiar with MS medications and how they are used in practice for differing forms of the disease.

When treating MS there are many different approaches to the intensity of treatment. What are the risks and benefits of starting a patient on self-injected interferon therapy versus infused immunotherapy? Compare and contrast the decrease in MS symptoms and relapses with these therapies in respect to the adverse medication reactions seen with the same therapies. What adverse medication reactions are more common as years on treatment accumulate?

INTRODUCTION

Multiple sclerosis (MS) is a central nervous system (CNS) inflammatory disease that affects approximately 1 in 450 per 100,000 females and fewer males in the United States.[1] The term “multiple sclerosis” refers to two characteristics of the disease: multiple neurologic symptoms that accrue over time

and characteristic plaques or sclerosed areas seen in numerous areas of the brain and spinal cord.

1 MS was first described more than 140 years ago, but the cause remains a mystery, and a cure is still unavailable. However, many recent advances in disease treatment and complication management have improved the quality of life of affected individuals.

EPIDEMIOLOGY

MS affects approximately 2.3 million people worldwide[2] and is usually diagnosed between 15 and 50 years of age, with a peak incidence occurring in the fourth decade. However, MS can occur in young children and significantly in older adults. While females are afflicted more than males by a ratio of 2.8:1, males usually develop the first signs of MS at a later age and are more likely to develop a progressive form of the disease. The rising incidence of MS in females may be associated with urbanization.[2] Additionally, MS occurs more frequently in Whites of Scandinavian ancestry compared to other ethnic groups.[3]

The factors most important in determining disease risk are geography, environmental influences, age, and genetics (discussed under etiology).[1,4-7] In general, MS is more prevalent above the 37th parallel, although recent studies suggest a waning latitude gradient as demonstrated by a substantial increase in Mediterranean regions. An inverse relationship between MS risk and 25-hydroxyvitamin D levels has been proposed.[8]

ETIOLOGY

The exact cause of MS is unknown but is thought to develop in genetically susceptible individuals exposed to random events and environmental factors that trigger immune-mediated CNS damage. Genetic variation accounts for approximately 30% of the overall disease risk, and more than 100 distinct genetic regions are associated with MS, collectively explaining about one-third of its genetic component.

The familial recurrence rate of MS is approximately 5%, with siblings being the most commonly reported relationship,[6] and monozygotic twins displaying a concordance rate of roughly 25%. Genes that lie within the major histocompatibility complex (MHC), on the sixth chromosome,[1,6] as well as interleukin-2α (IL-2α) and interleukin-7α (IL-7α) receptor genes have been associated with disease risk.[9-11] A genetic-environmental interaction is also reported for the human leukocyte antigen (*HLA*) *DRB1*1501* variant.[12] African Americans are less likely to be diagnosed with MS compared with Whites. However, emerging evidence suggests they are more likely to have a severe disease course and respond less to interferon (IFN) therapy.[13,14] A locus on chromosome 1 may be associated with increased susceptibility in African Americans.[15]

While genetics plays a role in overall disease risk, nongenetic factors such as geography, vitamin D deficiency, smoking, high dietary sodium, circadian disruption, human cytomegalovirus (CMV), the Epstein–Barr virus (EBV), and human herpesvirus-6 have been implicated in MS variably. In genetically susceptible individuals who live in a high-risk area for at least 2 years before age 15, the risk of MS is high, especially if exposed to an environmental factor. However, if they move from a high- to a low-risk area before age 15, they can acquire the low-risk status, while moving after age 15 can result in persistence of the high-risk status.[6] Smoking cigarettes has been associated with both an increased risk of developing MS and more severe progression of disability.[11,16] Excess body weight is also associated with a higher risk of developing MS.[17]

Although clear associations have not been identified, certain viruses might participate in the pathogenesis of MS by initiating or activating autoreactive immune cells in genetically susceptible individuals, leading to subsequent demyelination. Evidence supporting a viral etiology includes increased immunoglobulin G (IgG) synthesis in the CNS and increased viral antibody titers. Epidemiologic studies also indicate pathogen exposure in childhood, suggesting “viral” infections may precipitate exacerbations. In addition, data from both humans and experimental animal models suggest that viral infections with incubation periods cause disease with prolonged myelin destruction and a relapsing-remitting course.[1,18] The greatest evidence supports EBV, as autoreactive T cells could be activated by EBV through molecular mimicry due to sequence similarities between EBV and self-peptides. Other potential mechanisms of demyelination include enhanced breakdown and presentation of self-antigens, expression of viral superantigens, or bystander activation.[19] Antibody titers to Epstein–Barr nuclear antigen (EBNA) complex are higher in patients with MS versus controls and are associated with disease risk depending on sample collection time. Antibodies to specific epitopes within EBNA-1 can result in a 24-fold increased disease risk.[19] In addition, anti-EBNA titers are associated with RRMS, conversion of CIS to clinically definite multiple sclerosis (CDMS, confirmed diagnosis of MS), and with MRI measures such as gadolinium-enhancing lesions, change in T2-lesion volume, as well as the EDSS. Anti-EBNA and anti-

vascular cell adhesion (anti-VCA) titers are also associated with gray matter atrophy in MS.[20] Evidence of active EBV infection, which in time resolves, may lead to EBV-infected B cells being present in postmortem brain tissue of patients diagnosed with MS[21]; however, these findings have not been implicated.[22] Given all of this, most data suggest that EBV exposure is associated with MS development but does not support the concept of active EBV or aborting infection as directly causing MS.

PATHOPHYSIOLOGY

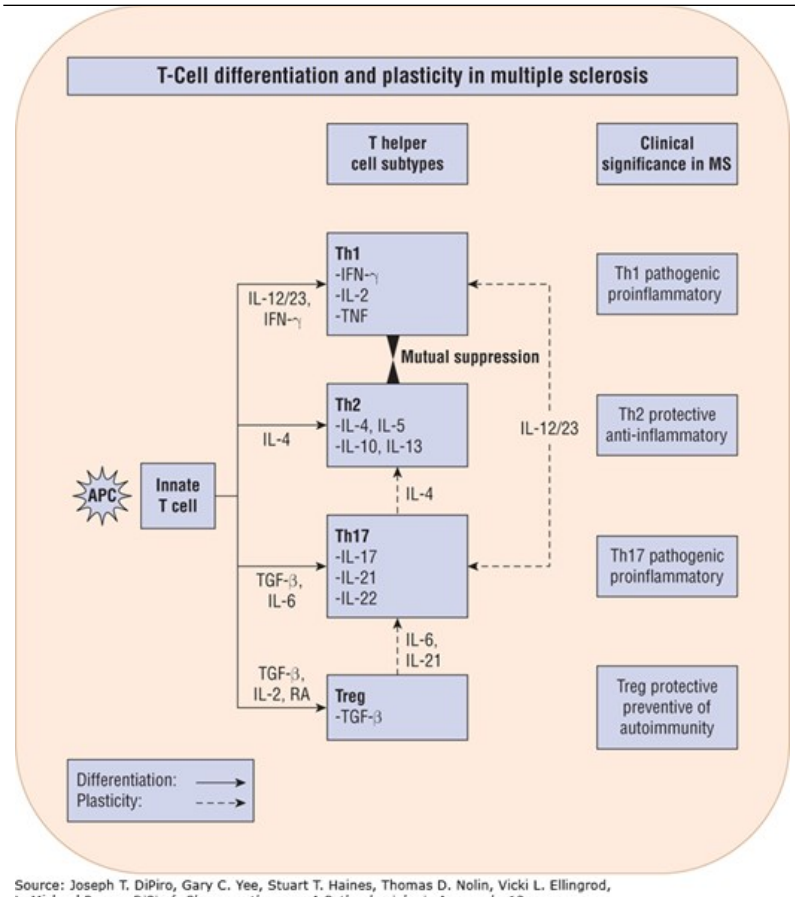
An important prominent feature of early-stage MS is immune cell infiltration from the periphery to the CNS, as immune cells enter the CNS parenchyma by crossing the blood–brain barrier, the subarachnoid space, or the choroid plexus across the blood-cerebrospinal fluid (CSF) barrier. Other proposed mechanisms include the "inside out" model where disease progression is a neurodegenerative process, similar to primary-progressive multiple sclerosis (PPMS) and secondary-progressive multiple sclerosis (SPMS), where the antigenic constituents are released from the CNS into the periphery, causing the inflammatory response.

2 Once in the CNS, immune cells promote neurodegeneration by stripping the myelin sheath surrounding CNS axons through an inflammatory, perivenular infiltrate consisting of T and B lymphocytes, macrophages, antibodies, and complement.[18] Demyelination renders axons susceptible to damage, which becomes irreversible when they are severed. Irreversible axonal damage correlates with disability and can be visualized as hypointense lesions, or "black holes," on T1-weighted MRI.[23,24]

Peripheral immune cells, along with activated CNS-resident microglia and astrocytes, promote demyelination and oligodendrocyte, and neuroaxonal injury. This is mediated through direct cell contact and the actions of soluble inflammatory and neurotoxic mediators; however, the exact trigger for T-cell activation in the periphery remains unclear, but T cells in MS patients recognize myelin basic protein (MBP), proteolipid protein, myelin oligodendrocyte glycoprotein, and myelin-associated glycoprotein. T-helper subtypes can be either pathogenic or protective in MS. One theory holds that specific T-cell subsets are not terminally differentiated but instead engender a level of plasticity that allows for their conversion from pathogenic to protective and vice versa under certain conditions (Fig. 74-1).[25]

FIGURE 74-1

Upon interaction with an antigen-laden APC and specific cytokines, the innate T cells undergo differentiation into a few lineages (subtypes). Four subtypes significant for MS pathophysiology are illustrated here (Th1, Th2, Th17, and Treg). Th1 and Th17 are proinflammatory, Th2 is anti-inflammatory, and Treg is regulatory. Th1 and Th2 are mutually suppressive and are relatively stable differentiated subtypes. In contrast, Th17 and Treg subtypes exhibit "plasticity" in that they can undergo phenotypic conversion to another T-cell subtype (Th1 or Th2) in the presence of specific cytokine conditions. This plasticity of Th17 and Treg is the immunologic basis for development of therapeutic agents to favor the production of suitable Th subtypes for combating microbial invasion and also concurrently achieving neurocellular recovery after an infection.[25] (APC, antigen presenting cell; Th, T-helper cell.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

A new concept of T-cell entry into the CNS suggests that the initial lymphocyte invasion may proceed through the ventricles toward the choroid plexus along a gradient that attracts activated Th17 (T-helper) cells.[26] The actual mediator of myelin and axonal destruction has not been established but may reflect a combination of macrophages, antibodies, destructive cytokines, and reactive oxygen intermediates. In patients with stable or mild disease, an increase in the number of cells that express messenger RNA (mRNA) for transforming growth factor-β (TGF-β) and interleukin-10 (IL-10) has been found compared with patients with severe disease. Conversely, a reduction in the number of T-regulatory (Treg) cells, which exhibit suppressor activity, is also associated with active MS and can be found in patients with progressive disease. It should be noted that ratios between various T cells (Treg ratios) do not always correlate with disease activity and that experimental evidence associates high 25-hydroxyvitamin D levels with improved Treg function, favoring the Th2 phenotype in the Th1/Th2 balance.[27] Finally, an immunological hallmark of MS is the intrathecal synthesis of multiple immunoglobulin clones with uncertainty regarding the antigen(s) against which they are directed.[28] Therefore, the complex interplay of various cells, antibodies, and cytokines remains to be elucidated.

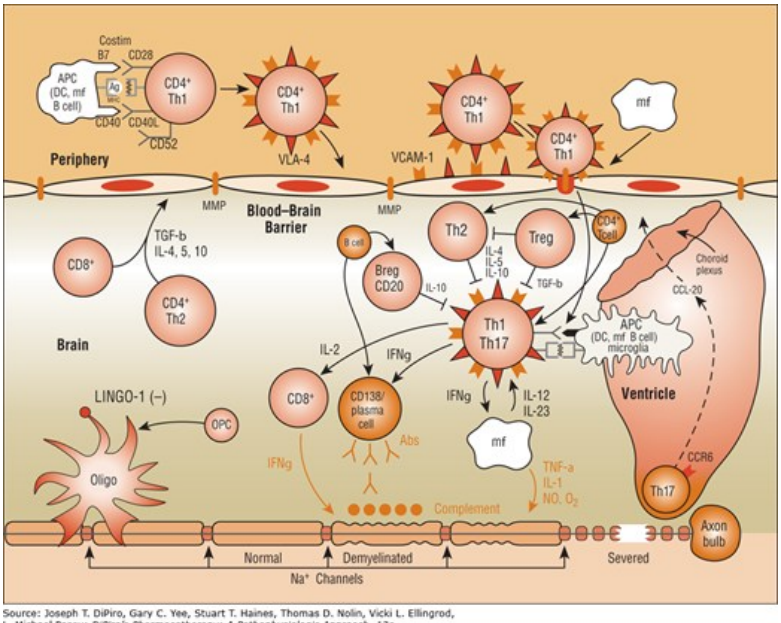
It is well accepted that MS lesions are heterogeneous, which may be due to differences in the stage of evolution of the lesions over time, differences in underlying immunopathogenesis, or a combination. Acute lesions show demyelination and axonal destruction with lymphocytic activity consistent with an inflammatory state. In contrast, chronic lesions display less inflammatory lymphocytes with active remyelination.[18] As the disease progresses, immune cell infiltration wanes, perhaps due to adaptive immune cell exhaustion from chronic antigen exposure. However, chronic CNS-intrinsic inflammation and neurodegeneration continue independent of peripheral immune activation. Consequently, meningeal tertiary lymphoid-like structures, which have been documented explicitly in secondary progressive disease, may contribute to late-stage inflammation in patients with this form of MS. In general, the relapsing phases of MS are more inflammatory[29] compared to the progressive forms of MS, where you see more neurodegeneration leading to long-term disability.

Although traditional descriptions focus on the white matter as the sole location of MS lesions, recent studies have identified cortical and subcortical gray matter lesions both pathologically[30] and radiographically.[31] In addition, a subset of patients with progressive MS are noted to have abnormalities consistent with B-cell follicles in the meninges.[32]

Just as the full dimensions of the neuropathology are uncertain, so is the pathogenesis of the MS lesion. However, substantial evidence suggests an autoimmune process directed against myelin and oligodendrocytes, the cells that make myelin[18] (Fig. 74-2).

FIGURE 74-2

Autoimmune theory of the pathogenesis of multiple sclerosis (MS). In MS, the immunogenic cells tend to be more myelin-reactive, and these T cells produce cytokines mimicking a Th1-mediated proinflammatory reaction. T-helper cells ($CD4^+$) appear to be critical initiators of myelin destruction in MS. These autoreactive $CD4^+$ cells, especially of the T-helper cell type 1 (Th1) subtype, are activated in the periphery, perhaps following a viral infection. The activation of T- and B-cells requires two signals. The first signal is the interaction between MHC and APC (macrophage, dendritic cell, and B cell). The second signal consists of the binding between B7 on the APC and CD28 on the T cell for T-cell activation. Similarly, CD40 expressed on APCs and CD40L expressed on T cells interact with signaling the proliferation of B cells within the blood–brain barrier following the entry to T cells. The T cells in the periphery express adhesion molecules on their surfaces that allow them to attach and roll along the endothelial cells that constitute the blood–brain barrier. The activated T cells also produce MMP that help create openings in the blood-––brain barrier, allowing entry of the activated T cells past the blood–brain barrier and into the CNS. Once inside the CNS, the T cells produce proinflammatory cytokines, especially interleukins (ILs) 1, 2, 12, 17, and 23, tumor necrosis factor-α (TNF-α), and interferon-γ (INF-γ), which further create openings in the blood–brain barrier, allowing entry of B cells, complement, macrophages, and antibodies. The T cells also interact within the CNS with the resident microglia, astrocytes, and macrophages, further enhancing the production of proinflammatory cytokines and other potential mediators of CNS damage, including reactive oxygen intermediates and nitric oxide. The role of modulating, or downregulating, cytokines such as IL-4, IL-5, IL-10, and transforming growth factor-β (TGF-β) also has been described. These cytokines are the products of $CD4^+$, $CD8^+$, and Th1 cells.[9] New pathogenic mechanisms involve, but are not limited to, receptor-ligand–mediated T-cell entry via choroid plexus (CCR6-CCL20 axis),[26] coupling of key receptor-ligands for inhibition of myelination/demyelination (LINGO-1/NOGO66/p75 or TROY complex, Jagged-Notch signaling). (Ag, antigens; APC, antigen presenting cell; DC, dendrite cell; IgG, immunoglobulin G; MΦ, macrophage; Na^+, sodium ion; MMP, matrix metalloproteinases; MHC, major histocompatibility complex; OPC, oligodendrocyte precursor cell; VLA, very late antigen; VCAM, vascular cell adhesion molecule.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Multiple Sclerosis

General

- Most patients with MS present with nonspecific complaints.

Primary Symptoms/Signs

- Visual complaints/optic neuritis
- Gait problems and falls
- Paresthesias
- Pain
- Spasticity
- Weakness
- Ataxia
- Speech difficulty
- Psychological changes
- Cognitive changes
- Fatigue
- Bowel/bladder dysfunction
- Sexual dysfunction
- Tremor

Laboratory Tests

- MS is a diagnosis of exclusion
- MRI
- CSF studies
- Evoked potentials

Secondary Symptoms

- Recurrent UTIs
- Urinary calculi
- Decubiti and osteomyelitis
- Osteoporosis
- Respiratory infections
- Poor nutrition
- Depression

Tertiary Symptoms

- Financial problems
- Personal/social problems
- Vocational problems
- Emotional problem

3 The clinical presentation of MS is extremely variable among patients and over time and is impacted by multiple external factors. The signs and symptoms are divided into three categories. Primary symptoms are a direct consequence of conduction disturbances produced by demyelination and axonal damage and reflect the damaged CNS area. Secondary symptoms are complications resulting from primary symptoms; for example, urinary retention, a primary symptom, can lead to frequent urinary tract infections (UTIs), a secondary symptom. Lastly, tertiary symptoms relate to the effect of the disease on the patient's everyday life.[33]

The clinical course of CDMS is classified into three categories: (1) RRMS, (2) SPMS, and (3) PPMS.[34] At symptom onset, about 85% of patients have relapses/exacerbations, with new symptoms lasting at least 24 hours and separated from other new symptoms by at least 30 days, followed by complete or incomplete remission. Exacerbations are referred to as relapses or attacks. This course is called RRMS, which is characterized by CNS inflammation. The first clinical presentation of RRMS is typically CIS, which is not a definite form of MS. During the RRMS phase, new brain MRI lesions correlate with clinical attacks, but typically, there are more new MRI lesions than new clinical symptoms. In RRMS patients, attack frequency tends to decrease over time and becomes independent of the development of progressive disabilities.[35] Neurologic recovery following an exacerbation is often quite good early in the disease course, but recovery following repeated relapses is not as complete. A new concept of a radiologically isolated syndrome (RIS) refers to individuals who have an MRI scan done for other reasons (eg, headache) and have radiological signs suggestive of MS. This is not a form of definite MS; however, over time, a percentage of these patients convert to RRMS.[36] When to start DMT remains unclear and varies by practice.

Approximately 10% to 20% of RRMS patients have a benign course (a retrospective diagnosis), characterized by few relapses that are often sensory in nature with minimal disability over time. Most RRMS patients (not with benign disease) eventually enter a progressive phase, referred to as SPMS, in which attacks and remissions are challenging to identify. Disability tends to accumulate more significantly during this phase of the illness. Additionally, new brain MRI lesions, especially those only seen with contrast media, are less common, and brain atrophy and T1 holes increase.[37]

4 Approximately 15% of patients never have discrete phases of attacks and remissions but rather have progressive disease from the outset, known as PPMS. These patients will have symptoms, especially spastic paraparesis, that may or may not worsen rapidly over time and accrue progressively more disability. Patients with PPMS are often diagnosed at later ages, with the number of males roughly equal to females. In general, PPMS patients tend to have a worse prognosis than those initially presenting with RRMS, although progression is variable.[38] A significant portion of patients with PPMS do not receive benefits from studied therapies, although ocrelizumab (Ocrevus) is FDA-approved for PPMS.[39] Both PPMS and SPMS are characterized as neurodegenerative processes. Previously, a small percentage of patients were classified as having a mixture of both progression and relapses, referred to as progressive-relapsing multiple sclerosis (PRMS), but since they are generally treated as relapsing patients, this nomenclature is no longer used.

The most widely used clinical rating scale is the EDSS, which uses a numerical value ranging from 0 (no disability) to 10 (death) to evaluate neurologic functions.[40] However, this scale is relatively insensitive to clinical changes not involving impairment of ambulation, such as fatigue, cognition, and affect. Other tools, such as the multiple sclerosis functional composite (MSFC), are being evaluated as a more sensitive measure for changes in MS-related disability over time.[41] Increasingly, MRI is used as an index of both disease activity and progression[18] with new lesions appearance or changes in lesion number, size, and volume used as outcome measures in research studies. Optical coherence tomography measures the retinal neural fiber layer thickness and may also be a measurable sign of pathological progression over time.[42]

The unpredictable nature of MS makes it impossible to anticipate exacerbations. However, certain factors, including infections, heat (including fever), sleep deprivation, stress, malnutrition, anemia, concurrent organ dysfunction, exertion, and childbirth, may aggravate symptoms or lead to an attack.

Interestingly, patients experience a significant reduction in relapses during the third trimester of pregnancy, followed by a relative increase postpartum.[43]

Between 60% and 80% of individuals diagnosed with MS have been reported to be sensitive to environmental heat, as temperature influences nerve impulses that are blocked or slowed down in a damaged nerve. Clinically, increased body temperature might worsen previous neurological deficits, including fatigue and decreased muscular endurance. Blurred vision, known as Uhthoff's phenomenon, is caused by increased body temperature due to physical exercise or physical restraint; however, these signs and symptoms improve or disappear after temperature normalization.

Multiple sclerosis does not directly diminish life expectancy. However, the development of secondary complications such as pneumonia or septicemia (secondary to aspiration in those with swallowing difficulties, decubitus ulcers, or UTIs), or rapid progression of primary lesions affecting respiratory function, can lead to a shorter than expected life span. Most life span decreases are seen in patients with rapidly progressive disease. Suicide rates in MS patients have been reported to be significantly higher than that seen in the general population.[44] The clinical and demographic factors used to predict prognosis are listed in Table 74-6.[7,42]

Diagnosis

5 Multiple sclerosis is a diagnosis of exclusion as symptoms can frequently be attributed to other neurologic diseases, just as many syndromes can mimic MS. The diagnosis remains primarily a clinical one that requires demonstration of "lesions separated in space and time." This terminology refers to the occurrence of at least two episodes of neurologic disturbance, which reflect specific sites of CNS damage that cannot be explained by other mechanisms.[47] The McDonald criteria, established by an international panel of MS experts,[47] allow for three diagnostic categories which include (1) MS, (2) possible MS (for those individuals at high risk of developing MS), and (3) not MS. These criteria aid in earlier diagnosis compared to older criteria,[45] as they may be somewhat more sensitive and equally specific.[46,48,49] Key to diagnosis is an MRI which is endorsed by the American Association of Neurology consensus panel.[50] In addition to brain MRI lesions, CSF abnormalities, and visual-evoked potential (VEP), studies may be substitutes for clinical lesions in defining "separated in space and time." The 2017 updated McDonald criteria allow for an earlier diagnosis in patients with CIS to establish "dissemination in space and time" with a single MRI.[47] Therefore, patients only need to have lesions in different CNS areas with at least one enhancing lesion that correlates with clinical symptomatology to fulfill these criteria and be diagnosed with CDMS. As an example, several immunotherapies are US FDA-approved for use after a single attack (CIS) of demyelination in the context of an appropriately abnormal brain MRI.

Laboratory Studies

To date, there are no tests specific for MS but rather, evidence is gathered through (1) MRI of the brain and spine,[50,51] (2) CSF evaluation examining for increased oligoclonal bands and increased IgG, (3) evoked potentials,[45,47] and (4) optic coherence tomography.[52] These should all be used in conjunction with the physical examination and history in establishing the diagnosis. Of these tests, MRI is the most valuable diagnostic tool as the brain and spine images reflect damage characteristic of MS plaques in multiple areas of the CNS. Therefore, MRI is the preferred technique for establishing a diagnosis, prognosis, and determining disease progression. Optic neuritis, a lesion or lesions on the optic nerve, is a common first symptom of MS. A more significant number of T2-weighted lesions (called *T2 burden of disease*) on MRI following optic neuritis or CIS appears to correlate with the development of disability and progression to CDMS.[51] Through the use of the contrast agent gadolinium, new lesions and disruptions of the blood −brain barrier can be determined and are associated with early conversion to CDMS in CIS patients.[51,53] However, these gadolinium-enhanced lesions do not correlate well with disability progression when examined over time, while brain atrophy, even early in the course of the illness, probably correlates better.[50]

Differential Diagnosis

Because many disorders can mimic MS, most patients are first screened with blood tests for rheumatologic, collagen-vascular, infectious, and sometimes inherited metabolic diseases. Additionally, electromyography may help in diagnosing amyotrophic lateral sclerosis and neuropathies.

Magnetic resonance imaging is used to rule out tumors and cervical spondylosis and may also lead to MS evaluations for many patients with little or no clinical history of MS. While some patients may have MRI scans suggestive of MS (so-called RIS), most have nonspecific scans with identifiable causes for their symptoms, including age greater than 50 years, hypertension, and migraine.[54] The use of established criteria for distinguishing MS lesions

from other etiologies enhances diagnostic accuracy.

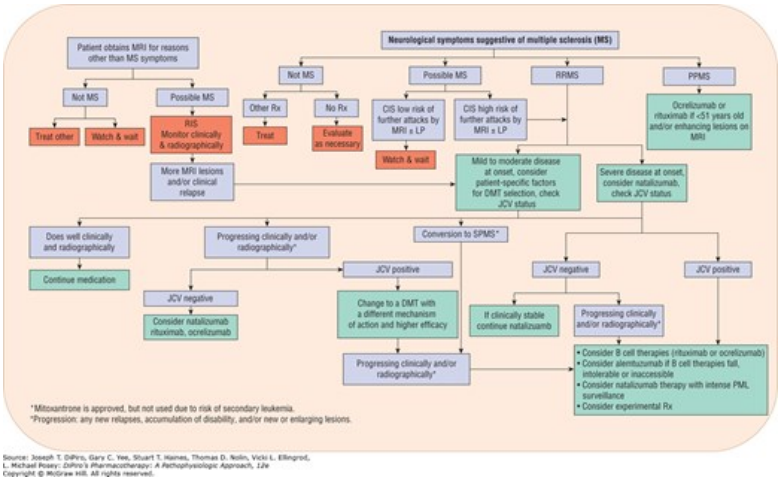
TREATMENT

Treatment of MS falls into three broad categories: (1) treatment of exacerbations, (2) disease-modifying therapies (DMTs), and (3) symptomatic therapies. While treatment of exacerbations will shorten the duration and possibly decrease the severity of the attack, the DMTs can alter the course of the illness and diminish progressive disability over time; however, symptomatic disease management is of utmost importance to maintain quality of life. Although different treatment modalities have been studied in the last 30 years, older trials are flawed, and as such, there are no universally accepted treatment algorithms for MS. In 2018 the American Academy of Neurology (AAN) released DMT practice guidelines for adult MS. One potential algorithm for the immunotherapy of CDMS is shown in Fig. 74-3.[55] The Consortium of Multiple Sclerosis Centers also put out guidelines on treatment selection based on patient-specific factors.[56] However, treatment recommendations often vary among clinicians and centers, and decisions are frequently based on the wishes and goals of individual patients.

FIGURE 74-3

Algorithm for management of clinically definite multiple sclerosis. (MRI, magnetic resonance imaging; LP, lumbar puncture; MS, multiple sclerosis; CIS, clinically isolated syndrome; JCV, John Cunningham virus, PML, progressive multifocal leukoencephalopathy; RRMS, relapsing-remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; Rx, prescription medication; DMT, disease modifying therapy.)

Adapted from References 55 and 56.



Desired Outcomes

The main treatment goals are to improve the overall quality of life, maintain employment, and minimize long-term disability for MS patients. Disease-related treatment goals include reducing exacerbations or relapses, decreasing the number of white matter lesions and black holes on MRI, averting brain atrophy, and ultimately halting disease progression. Both treatment and disease-related goals can be obtained with early disease recognition and immediate utilization of FDA-approved DMTs.

General Approach to Treatment

The severity of symptoms at initial presentation will determine whether an induction or escalation algorithm is assigned to an individual patient. When currently available FDA-approved medications do not alter natural disease progression, investigational agents or non–FDA-approved medications, such as rituximab, may be used. The use of escalation approaches early in the disease course with safer yet partially effective medications is thought to be helpful.

MS unfortunately often affects individuals in their most productive years of life. Therefore, practitioners must help patients set realistic expectations

over their lifetime by developing long-term treatment and management plans. Throughout this illness, patients are likely to acquire secondary and tertiary MS symptoms. In clinical trials, high nonadherence rates are a factor in treatment failure. Nonadherence may occur due to perceived lack of treatment benefit, cost, adverse effects, depression occurrence, complicated dosing, and/or undesirable routes of administration (eg, subcutaneous, intramuscular injection, intravenous [IV]). Figure 74-3 represents a clinical algorithm for the treatment of MS.[55]

Nonpharmacologic Therapy

Medications are the primary mainstay of MS treatment. Still, patients may find occupational therapy beneficial to improve the activities of daily living or learn new techniques or tools to accomplish these tasks and remain active. Furthermore, physical therapy may improve muscle strength to improve their gait and balance, and stretching exercises reduce muscle spasms or help mobility through aids such as canes or walkers.

Pharmacologic Therapy

Treatment of Exacerbation

Exacerbations are the hallmark of early RRMS. Although recovery after relapses is generally complete, continued relapses over time may be associated with a substantial accumulation of disability. Frequent relapses (more than three relapses per year in the first 2 years after diagnosis) have shown a consistent positive correlation with developing neurological disability later. However, mild exacerbations that do not produce functional decline may not require treatment. Therefore, decisions to treat relapses are usually substantiated by patient expectations, prior experience with corticosteroids, and predicted course of recovery. Accepted treatment indications for relapses that are (1) mono- or polysymptomatic presentations; (2) relapses that localize to the optic nerve, spinal cord, or brainstem; (3) those with functional limitations that affect activities of daily living; and (4) symptoms that worsen over a 2-week period. An IV injection of high-dose corticosteroids such as methylprednisolone is recommended by the AAN when functional ability is affected.[55] While corticosteroid mechanism of action in MS is unknown, they may improve recovery by decreasing edema in the area of demyelination. In particular intravenous methylprednisolone can shorten the exacerbation duration and also potentially delay repeat attacks for up to 2 years after optic neuritis,[55] although it does not definitively affect disease progression.[57]

According to clinical response, methylprednisolone doses range from 500 to 1,000 mg/day, given IV for 3 to (rarely) 10 days. In initiated within 2 weeks of symptom onset, the functional recovery after an exacerbation is more rapid, with improvement usually beginning after 3 to 5 days. Short-term steroid use is often accompanied by sleep disturbance, a metallic taste in the mouth, and rarely gastrointestinal (GI) upset. Patients with diabetes mellitus or a predilection to diabetes mellitus may have significant elevations of blood sugar, requiring the use of insulin. Intravenous methylprednisolone therapy is associated with acne and fungal infections, mood alteration, and, rarely, GI hemorrhage (especially in hospitalized patients or in those taking aspirin) when administered for longer durations. Equipotent doses of oral prednisone or dexamethasone can be substituted for IV methylprednisolone, although dexamethasone use is not well supported in the literature. Although adrenocorticotropic hormone (ACTH) is the only FDA-approved agent for MS exacerbation treatment, it is rarely used due to cost and availability.

A small number who experience a relapse of MS will have more severe attacks, manifested by hemiplegia, paraplegia, or quadriplegia. If improvement with aggressive steroid therapy is not seen, plasma exchange (PLEX) every other day for seven treatments can be beneficial for approximately 40% of patients, or intravenous immunoglobulin can be given.

A “pseudoexacerbation” must be ruled out before exacerbation treatment is initiated or DMTs are altered. Within this context, a “pseudoexacerbattion” occurs when symptoms occur for less than 24 hours or are precipitated by something other than the natural course of the disease, such as heat, infections (eg, UTIs), or stress (emotional or physical).

Disease-Modifying Therapy

Table 74-1 shows the indications and dosing of DMTs. Medications used to treat MS are either immunomodulatory (ie, alter the immune signals without cytotoxic effect or bone marrow suppression) or immunosuppressive (ie, alter the immune system through a direct cytotoxic activity or bone marrow suppression). These drugs, however, have a higher risk-to-benefit ratio based on their safety profile when used later on in therapy.[29] The current FDA-approved first-generation therapies are self-injected medications that decrease annualized relapse rate by about 30% and decrease the formation of new white matter lesions. These include four interferon (IFN) formulations and glatiramer acetate (a non-IFN). The first-generation DMTs are not immediately effective for symptoms, but rather their efficacy may be seen approximately 1 to 2 years after starting therapy. In addition to the

first-generation DMTs, the FDA has also approved ocrelizumab, natalizumab, mitoxantrone, fingolimod, siponimod, ozanimod, ponesimod, teriflunomide, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, cladribine, ofatumumab, and alemtuzumab for the treatment of relapsing forms of MS. Ocrelizumab is also FDA-approved for PPMS, and mitoxantrone has an additional FDA indication for progressive or worsening MS. These therapies are considered specialty medications and are only available through specialty pharmacies at a yearly cost of upwards of $100,000. This cost does not include nursing, pharmacy, and technical fees, especially for the infusion medications that require administration in an outpatient facility under medical supervision.

In some patients with poor prognostic factors and poor clinical presentation, ocrelizumab, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate may be prescribed as initially instead of starting a first-generation DMT associated with less serious side-effect risk. This practice would be considered an induction therapy, where all therapeutic efforts concentrate in the early phases of the disease.

The efficacy of the DMTs may vary considerably between individual patients and for any given patient at different time points. Moreover, patients may have different adverse medication effects or risk tolerance and preferences regarding the administration route. Therefore, access to the full range of therapeutic options is critical for decision making between patients and their clinicians. Table 74-2 outlines adverse medication reactions and monitoring parameters of DMTs.

Interferon-β_{1b} and Interferon-β_{1a}

IFN-β_{1b} (Betaseron, Extavia) was the first agent proven to favorably alter the natural course of the illness (Table 74-7).[57] Although its mechanism of action is unknown, it does exert immunomodulating properties, including augmentation of suppressor cell function, reduced IFN-γ secretion by activated lymphocytes, its macrophage-activating effect, and its ability to downregulate the expression of IFN-γ-induced class II MHC gene products on antigen-presenting glial cells. Additionally, IFN suppresses T-cell proliferation and may decrease blood–brain barrier permeability by reducing matrix metalloproteinases.[57] IFN-β also increases the production of regulatory CD56 (bright) natural killer cells and Treg cells.[60] In general, all IFNs exert these actions in the periphery and at the blood–brain barrier level.

TABLE 74-7

Evidenced-Based Recommendations for Disease-Modifying Treatment of Multiple Sclerosis

Recommendations	Recommendation Grades*
Interferon-β	
• Interferon-β has been shown to reduce attack rates in patients with MS or those with CIS who are at high risk of developing MS	A-I
• It is appropriate to consider IFN-β for any patient with clinically definite MS or who already has RRMS or SPMS and is still experiencing relapses	A-I
• The effectiveness of IFN-β in patients with SPMS but without relapses is uncertain	U-I
• Route of administration of IFN-β products is probably not clinically important with regards to efficacy; however, the side-effect profile does differ	B-II
• Rate of production of neutralizing antibodies is probably less with IFN-β_{1a} than with IFN- β_{1b}	B-I
• Presence of neutralizing antibodies may be associated with a reduction in the clinical effectiveness of IFN-β treatment	C-I

Glatiramer acetate	
• Glatiramer acetate has been shown to reduce the attack rate in patients with RRMS	A-I
• Treatment with glatiramer acetate may slow sustained disability progression in RRMS	C-I
Mitoxantrone	
• Mitoxantrone probably reduces the attack rate in patients with relapsing forms of MS	B-II, III
• Mitoxantrone may have a beneficial effect on disease progression in MS	C-II, III
Natalizumab	
• Natalizumab decreases clinical relapse rate, gadolinium-enhancing lesions, and new T2 lesions	A-I
• Natalizumab in RRMS positively changes measures of disease severity such as EDSS progression rate and changes lesions on MRI in RRMS	A-I
Ocrelizumab	
• Ocrelizumab in PPMS is shown to decrease confirmed disability progression, lessen worsening of timed 25-ft (~7.5-m) walk, decrease T2-weighted MRI lesions volume by 3.5%, and percentage of brain volume loss by 0.90%	A-I
• Ocrelizumab in RRMS positively changes measures of disease severity such as EDSS progression rate and changes lesions on MRI in RRMS	A-I

*Strength of recommendations: A: established; B: probable; C: possible; U: inadequate data to support recommendation.

CIS, clinically isolated syndrome; RCT, randomized controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis.

Quality of evidence: Class I, evidence from one or more prospective, randomized, controlled clinical trial; Class II, evidence from cohort or RCT not meeting criteria for class I; Class III, evidence from other controlled trials; Class IV, evidence from uncontrolled studies, case reports, case series, or expert opinion.

Data from References 60 and 62.

IFN-β_{1b} is a nonglycosylated synthetic analog of recombinant IFN-β produced in *Escherichia coli*. It is administered subcutaneously every other day at a dose of 250 mcg (8 million international units). Clinical trials have demonstrated that at these doses, IFN-β_{1b} significantly reduces the annual relapse rate and MRI burden of disease compared with placebo; however, no significant differences between the IFN and placebo were noted with respect to clinical disability.[60] Betaseron is packaged in partially premixed syringes that do not require refrigeration and can be used with an autoinjector. In 2009, Extavia was approved; however, this is the same medicinal product as Betaseron.

IFN-β_{1a} (Avonex, Rebif) is a natural-sequence glycosylated IFN produced in Chinese hamster ovary cells. Avonex is administered as a 30-mcg dose (6 million international units) intramuscularly once weekly and Rebif is given as either 22 or 44 mcg subcutaneously three times weekly. Both are supplied in a 0.5-mL prefilled syringe which should be refrigerated but is stable at room temperature for 30 days. Rebif may have lower immunogenicity and a

slightly better side-effect profile than Avonex.[61]

Patients receiving IFN-β_{1a} (Avonex) for 2 years demonstrated statistically significant reductions in annual relapse rates (by approximately one-third), as well as disease progression (defined as a confirmed decrease of one point on the EDSS), compared to placebo.[61] Patients receiving Avonex had significantly fewer new enhancing lesions on MRI compared with placebo, and similar results were seen with the higher dose of (44 mcg) of Rebif.[61] Other studies reveal Avonex's significant effects on slowing brain atrophy[62] and the progression of cognitive decline.[63] Therefore, these observations show that IFN-β possesses significant disease-modifying activity.

Pegylated IFN-β_{1a} (Plegridy) is FDA-approved for relapsing forms of MS. The attachment of polyethylene glycol (PEG) polymer chains to the interferon molecules result in a longer half-life and allows for less frequent dosing, as it is given by subcutaneous injections once every 2 weeks. Plegridy is associated with a significant reduction in annualized relapse rates (35.6%), new MRI lesions, risk of disability progression compared to placebo.[64]

All of the IFNs have similar adverse medication reactions, and CBCs, platelets, and LFTs should be documented at baseline, after 1 month of therapy, every 3 months for 1 year, and every 6 months thereafter. A small percentage of patients develop depressed blood cell counts that usually respond to therapy discontinuation. Transient elevations in liver enzymes can also be seen, which respond to treatment discontinuation. However, rare cases of liver failure requiring transplantation have been reported, which have resulted in package insert modifications for all IFN-β products to reflect this risk. Other more common adverse effects include injection-site redness and swelling, menstrual irregularities, and rarely injection-site necrosis. Injection-site reactions with IFN-β_{1b} are probably worse and can occur at any time. They can be lessened by rotating the injection site, using an autoinjector, using topical lidocaine, or applying ice before and after the injection. In addition, injecting the medications at body temperature (place under armpits to warm) will decrease injection-site pain.

Flu-like symptoms (eg, fever, chills, and myalgias) are seen in most patients and typically occur up to 24 hours after injection. These symptoms usually abate within 1 to 3 months after starting the injections; however, for some patients, they may persist. To alleviate these flu-like symptoms, patients may try taking the injection at bedtime to sleep through the most bothersome symptoms. They may also use a nonsteroidal anti-inflammatory agent or acetaminophen before and regularly for 24 hours after IFN-β administration. Using one-quarter or one-half the standard dose, with an increase to the full dosage over 1 to 2 months, is also beneficial in reducing flu-like adverse medication reactions.[65] Lastly, a short burst of oral prednisone can alleviate some adverse effects as this may suppress the transient immune activation that can occur following the introduction of IFN-β.[65]

Less common adverse medication reactions include transient shortness of breath or tachycardia, thyroid dysfunction, and neutralizing antibodies. All the IFNs, but especially IFN-β_{1b}, can produce depressive symptoms. Therefore, clinicians must monitor all patients carefully depressive symptoms and monitor closely for suicide risk. Most patients will not see MS symptom improvement when taking IFNs, and many will experience adverse medication reactions; thus, adherence is a significant issue.

Finally, safety data on IFN-β in pregnancy and lactation is lacking, and abortifacient activity in primates has been noted. Until adequate safety data are available, individuals who are biologically female and are able to get pregnant should be counseled to use appropriate contraception while using these products.

Glatiramer Acetate (Copaxone)

Glatiramer acetate (formerly known as copolymer-1) is a synthetic polypeptide consisting of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. Its precise mechanism of action is unknown, but it appears to mimic the antigenic properties of myelin basic protein (MBP).[66] This agent may act directly to MHC class II receptors and inhibit the binding of MBP peptides to T-cell receptor complexes.[66] Glatiramer acetate induces Th2 (anti-inflammatory) lymphocytes in experimental allergic encephalomyelitis,[66] which is thought to contribute to "bystander" suppression at the site of the MS lesion, resulting in reduced inflammation, demyelination, and axonal damage.[57] However, it may also suppress T-cell activation and recent studies suggest it has a neuroprotective effect by inducing brain-derived neurotrophic factor.[67]

Given subcutaneously, as a daily 20-mg or three times weekly 40-mg dose, glatiramer acetate, or its generic biosimilar, Glatopa appear to have a relatively mild adverse effect profile with mild injection site pain and pruritus being most common. Approximately 10% of patients experience a one-time transient reaction consisting of chest tightness, flushing, and dyspnea beginning several minutes after injection and usually lasting no longer than

20 minutes. This postinjection reaction occurs with any dose and is not limited to the first injection. If patients have no history or evidence of coronary artery disease, they may be assured these reactions are almost always self-limited and benign.

Glatiramer acetate has demonstrated significant reductions in mean annual relapse rate (approximately 29%), comparable with the IFNs and may slow the progression of disability in patients with RRMS.[65] It also delays the development of T1 holes on brain MRIs.[68] Long-term uncontrolled data show that it remains safe and effective for over 10 years.[69] Glatiramer acetate needs to be stored in the refrigerator but can be kept at room temperature for up to 1 week.

The FDA-approved Copaxone for the treatment of RRMS based on a placebo-controlled trial in treatment-naive patients that demonstrated significant reductions in mean annual relapse rate (approximately 34%), number of new T1 and T2 lesions, and similar safety profiles.[70] Recent studies show favorable adverse medication effects and convenience profiles, with comparable efficacy when patients were switched from glatiramer acetate 20 mg daily to 40 mg three times weekly.[71]

Natalizumab (Tysabri)

Natalizumab is a partially humanized monoclonal antibody directed at the cell surface adhesion molecule $\alpha_4\beta$-integrin (also known as very-late antigen 1, VLA-1). It works by attaching to VLA-1 and blocking its ability to interact with its ligand on CNS endothelium vascular cell adhesion molecule 1 (VCAM-1), resulting in activated lymphocytes that are denied entry past the blood–brain barrier.

Natalizumab significantly reduces the number of new gadolinium-enhancing lesions by more than 90%, diminished relapses by 60%.[72] Compared to placebo, natalizumab also significantly delayed disability progression.[73] When added to IFN-β_{1a} (Avonex), natalizumab reduced relapse rates by more than 50% and gadolinium-enhancing lesions by 84%, compared to patients who continued with IFN-β_{1a} alone.[74] In these trials, natalizumab was infused IV every four weeks and was relatively well tolerated, although approximately 1% of patients developed infusion reactions, and 6% developed neutralizing antibodies that diminished the efficacy of the medication.

Natalizumab is FDA-approved for use in relapsing forms of MS. Shortly after its approval, three patients were reported to have contracted progressive multifocal leukoencephalopathy (PML), a rare brain infection most commonly seen in patients with human immunodeficiency virus.[75-77] In response, the FDA issued a black-box warning about PML and required enrollment in a Risk Evaluation and Mitigation Strategy (REMS) program called TOUCH. While the estimated risk for PML is low, it is high compared to other MS treatments.[78] As of December 2017, natalizumab is correlated to 756 PML cases, with three factors impacting the overall risk; (1) duration of treatment (24 months or longer); (2) prior use of immunosuppressive therapies (mycophenolate mofetil, alemtuzumab, efalizumab, and rituximab); and (3) a history of anti-John Cunningham virus (JCV) antibodies.[79,80] Current recommendations are to screen patients at baseline and every 6 months with a JCV test while receiving natalizumab.[81] A two-step enzyme-linked immunosorbent assay (ELISA, STRATIFY TEST) is available for the qualitative detection of serum antibodies to the JCV, offering a false-negative rate of 2.5%.[79,80]

For those patients developing PML, a plasma exchange (PLEX) can help rapidly clear the medication from the blood.[82] An acute syndrome, referred to as immune reconstitution inflammatory syndrome (IRIS), is associated with acute neurological deterioration after PLEX, requiring high-dose steroids.[83] Natalizumab is generally reserved for patients with highly active disease or those who have not responded to more well-tolerated agents, given its risk profile.

Sphingosine-1-Phosphate Receptor Agonists (Fingolimod, Siponimod, Ozanimod, Ponesimod)

Fingolimod (Gilenya) was the first oral DMT approved for MS. It mechanistically acts as a sphingosine 1-phosphate (S1P) receptor agonist and exhibits its immunosuppressant properties by sequestering circulating lymphocytes into secondary lymphoid organs. Additionally, fingolimod also reduces the infiltration of T lymphocytes and macrophages into the CNS, resulting in neuroprotective effects. In clinical trials, it decreased annualized relapse rates by approximately 52% compared to IFN-β_{1a}, and 92% of patients were free of gadolinium-enhancing lesions after 7 years of continuous therapy. However, this data was obtained using the 1.25 mg dose, which is different from the FDA-approved dose of 0.5 mg once daily. Fingolimod is the first DMT to have a pediatric indication for children age 10 years and older. Siponimod (Mayzent) and Ozanimod (Zeposia) bind to S1P receptors 1 and 5

with higher affinity and Ponesimod (Ponvory) binds to the S1P receptor only, which makes these agents more selective than fingolimod, which binds to receptors 1, 3, 4, and 5.

Fingolimod is associated with pronounced first-dose bradycardia. Other rarer adverse medication reactions include bradyarrhythmia or atrioventricular block, infections, macular edema, a decrease in forced expiratory volume over 1 second in patients with previously compromised lung function, liver enzyme elevation, sustained 1 to 2 mm Hg increases in systolic and diastolic blood pressure, and lymphoma. All patients starting fingolimod should be monitored for signs of bradycardia for 6 hours after the first dose, including hourly pulse and blood pressure measurement. Additionally, ECG monitoring should start before dosing and continue until the end of the observation period or until all symptoms resolve. For patients at higher risk, this monitoring should continue longer than 6 hours, and in some cases, continue overnight. A new 6-hour observation period is required for patients who have discontinued and wish to restart therapy; however, this requirement varies depending on the days of missed treatment. Furthermore, extended monitoring is recommended for patients with certain preexisting conditions such as QT prolongation or those receiving concomitant medications that slow the heart rate or atrioventricular conduction, cause QT interval prolongation, or have a known risk for torsades. The following class Ia and class III antiarrhythmic agents are contraindicated for concurrent use with fingolimod: quinidine, procainamide, disopyramide, amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide, and dronedarone.[84] As of March 2018, PML has also been reported with fingolimod use in eight patients, which was seen after 3 years of exposure, and independent of natalizumab treatment.[78] Similar adverse events have been experienced in the pediatric population.

Since siponimod, ozanimod, and ponesimod bind more selectively to the S1P receptor, their labeling only requires first-dose observation for high-risk groups.[85,86] Additionally, ponesimod is a 4-hour first-dose observation compared to a 6-hour observation period.[87] Upon starting therapy, a slow titration is required for all three agents. However, siponimod also requires CYP2C9 genotype testing to determine dose adjustments or contraindications. For CYP2C9 genotypes *1/*1, *1/*2, or *2/*2, associated with normal metabolism, no dose adjustments are required. For CYP2C9 genotypes *1/*3 or *2/*3, associated with intermediate metabolism, a dose reduction is necessary, and siponimod is contraindicated for use in patients with a CYP2C9 *3/*3 genotype associated with poor metabolizer status.[85]

Additional monitoring recommendations for S1P receptor modulator use include baseline CBCs, LFTs, ophthalmologic examinations, and ECG in patients with known heart problems. Importantly, ketoconazole can increase the area under the curve of fingolimod by 70%. For patients requiring live vaccine administration (ie, Zostavax, Flumist, Measles, Mumps, and Rubella [MMR], Yellow Fever [YF-VAX]), consider doing so prior to starting fingolimod or waiting two months after discontinuation. Ozanimod should not be coadministered with CYP2C8 inhibitors, BCRP inhibitors, or strong CYP2C8 inducers.[86] Ponesimod leaves the blood in about 1 week if treatment needs to be stopped for any reason. This provides for flexibility if a patient needs vaccines, desires to start family planning, or has any infections that need to be addressed.[87]

Teriflunomide (Aubagio)

Teriflunomide is an oral immunomodulatory agent, the FDA approved for the treatment of relapsing forms of MS. The medication works by inhibiting dihydroorotate dehydrogenase to prevent the proliferation of peripheral lymphocytes (T and B cells). The reduction of activated lymphocytes within the CNS reduces inflammation and demyelination in patients with MS. Teriflunomide is the active metabolite of leflunomide, an agent approved for treating rheumatoid arthritis, and is dosed as 7 or 14 mg orally once daily.

In CDMS patients, teriflunomide (7- or 14-mg dose) resulted in a 31% reduction in annualized relapse rates and unique active lesions per MRI scan compared to placebo.[88] Disability progression was also reduced by almost 30% for those receiving 14 mg of teriflunomide daily.[89]

Although teriflunomide is not metabolized by CYP450 enzymes, it inhibits CYP2C8 and induces CYP1A2. This medication is also a substrate for the breast cancer–resistant protein (BCRP); therefore, inhibitors of BCRP (eg, cyclosporine) may increase serum concentrations of teriflunomide. Additionally, teriflunomide inhibits other organic anion transporters such as OATP1B1 and OAT3; however, the significance of these medication interactions is unknown at this time. Concomitant use of warfarin and teriflunomide resulted in a 25% decrease in the international normalized ratio (INR), necessitating close monitoring. When coadministered with estradiol and levonorgestrel, the mean maximum serum concentration and area under the curve are increased.

Terifluonomide's most common adverse effects are increases in LFTs, alopecia, nausea, diarrhea, influenza, headache, and paresthesia. Recommended monitoring includes monthly LFTs for the first 6 months due to teriflunomide's black-box warning related to hepatotoxicity risk.

Additionally, teriflunomide also has a black-box warning for teratogenicity, as animal studies linked oral teriflunomide with fetal malformations and embryo lethality in female rats, as well as reduced sperm count in male rats. Therefore, teriflunomide is contraindicated in pregnancy and in individuals of childbearing potential not using reliable contraception. During therapy or within 2 years after discontinuation, patients who become pregnant should enroll in the Aubagio Pregnancy Registry and consider a cholestyramine washout. Additionally, males may also consider a cholestyramine washout to reduce serum medication levels should their partner's pregnancy be desired, as this medication may remain in the blood for up to 2 years after discontinuation. Teriflunomide may activate tuberculosis, so a negative skin test or treatment of the disease must be documented prior to starting therapy.

Dimethyl Fumarate (Tecfidera), Diroximel Fumarate (Vumerity), and Monomethyl Fumarate (Bafiertam)

Dimethyl fumarate, diroximel fumarate, and monomethyl fumarate true mechanism of action is unknown; however, they are in vitro nicotinic acid receptor agonists and in vivo activators of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway that is involved in the cellular response to oxidative stress. Dimethyl fumarate and diroximel fumarate are both converted to the same active metabolite, monomethyl fumarate. These three DMTs are FDA-approved for relapsing forms of MS, including CIS, relapsing-remitting disease, and active secondary progressive disease in adults.

Esterases metabolize dimethyl fumarate in the GI tract, blood, and tissues with no known medication interactions. It is initially dosed at 120 mg (delayed release) orally twice daily. After 7 days, the dose is increased to 240 mg (delayed release) orally twice daily. Dimethyl fumarate decreases the annualized relapse rate by 44% to 52%.[90,91] Laboratory monitoring includes a CBC before starting therapy, 6 months later, and then annually. Adverse medication reactions include lymphocytopenia (2%-6%), increased LFTs, and flushing (40%), which are reduced by food intake and dissipate over 1 month. Four cases of PML are attributed to dimethyl fumarate use as of March 2018.[78] Rash, abdominal pain, diarrhea, nausea, and vomiting have also been reported, which decrease over 1 month and respond to symptomatic treatment; however, slowing the dose-escalation may reduce GI adverse medication reactions risk. Dimethyl fumarate has a pregnancy Category C classification.

Diroximel fumarate is dosed at 231 mg twice daily orally, increased to a maintenance dose of 462 mg (administered as two 231 mg capsules) twice daily after 7 days.[92] Monomethyl fumarate is dosed at 95 mg twice daily orally, increased to maintenance dose of 190 mg (administered as two 95 mg capsules) twice daily after 7 days.[93] Flushing associated with these agents can be reduced by coadministration with food or with 325 mg of a non-enteric-coated aspirin 30 minutes before dosing.[93] Both diroximel fumerate and monomethyl fumarate carry the same monitoring and laboratory recommendations as dimethyl fumarate, including PML risk. These agents also have a lower incidence of gastrointestinal symptoms compared to dimethyl fumarate.[94,95]

Cladribine (Mavenclad)

Cladribine is an oral DMT whose mechanism is thought to impair DNA synthesis, resulting in dose-dependent depletion of both B- and T-lymphocytes. It is a prodrug, activated through phosphorylation to 2-chlorodeoxyadenosine triphosphate (Cd-ATP). It is indicated to treat relapsing forms of MS to include relapsing-remitting disease and active secondary progressive disease in adults. Cladribine has been shown to significantly reduce the annualized relapse rate as 81% of patients in clinical trials did not replase. Additionally, cladribine reduces the time to 3-month confirmed EDSS progression and the median number of active T1 Gd+ lesions and active T2 lesions compared to placebo.[96]

It is administered in two treatment courses, which occur approximately 1 year apart from each other, and consist of two cycles of treatment for a total of four doses over 2 years. The maximum lifetime dose of cladribine is 3.5 mg per kg bodyweight which is 1.75 mg per kg per treatment course. The first treatment course has two cycles, the first dose is started anytime, and the second dose is administered 23-27 days after the first dose of the first course. The second-year treatment course is started approximately 1 year after the start of the first course, and the final dose of treatment should be administered 23 to 27 days after the first dose of the second-year course.[97]

Adverse medication reactions from treatment include increased risk of infection (including Tb, hepatitis B or C, shingles, and PML), liver injury, and heart failure. Cladribine requires a medication guide due to its adverse medication effect profile and increased risk of malignancies and teratogenicity. Treatment monitoring includes cancer screening, CBC, infection screening (including MRI for PML), and liver enzyme tests. It is not indicated for the treatment of CIS due to its severe adverse medication reactions, and therefore should be saved for use in patients who have had an inadequate response or cannot tolerate other DMTs.[97]

Alemtuzumab (Lemtrada)

Alemtuzumab is a humanized monoclonal antibody against CD52, a glycosylphosphatidylinositol-anchored protein consisting of 12 amino acids expressed at high levels on T and B lymphocytes, and to a lesser extent on monocytes, macrophages, and eosinophil granulocytes. Within a few minutes after infusion, alemtuzumab leads to depletion of CD52 positive cells through antibody-dependent cell-mediated cytolysis and complement-dependent cytolysis.

Alemtuzumab is FDA-approved for the therapy of RRMS. Compared to IFN-β_{1a} therapy alemtuzumab demonstrated a 50% reduction in relapses and a significant reduction in the 6-month accumulation of disability.[98,99] Additionally, MRI measures also proved alemtuzumab's superiority with significantly less gadolinium-enhancing lesions, new or enlarging T2 lesions, and brain atrophy.[98] Lastly, significantly more alemtuzumab than IFN-β_{1a}–treated patients were free of any clinical and MRI disease activity. Currently, alemtuzumab therapy is approved for two courses of treatment administered a year apart. In the first course, 12 mg is infused for 5 consecutive days and then for 3 days in the second course.

Alemtuzumab's high efficacy parallels its considerable high risk of infusion-associated reactions (IARs), affecting over 90% of patients.[100] Concomitant corticosteroids, antihistamines, and antipyretic medications can help avoid IARs. Other adverse medication reactions are commonly mild to moderate and consist of headache, rash, pyrexia, and nausea. Respiratory tract and UTIs are also common. During the clinical studies, the incidence of herpes infections led to the recommendation that prophylactic acyclovir treatment be implemented 0 to 4 weeks after alemtuzumab infusion to reduce infection rates significantly. Moreover, there are single case reports of spirochetal gingivitis, pyogenic granuloma, esophageal candidiasis, tuberculosis, and listeria meningitis. Thus, it is best to avoid unpasteurized cheeses while taking this medication.[100] PML has also been reported after the second alemtuzumab cycle; therefore, monitoring is warranted for all patients.[101]

Additional risks seen with alemtuzumab use include secondary autoimmune disease occurring in approximately 30% to 40% of patients, predominantly impairing thyroid function and manifesting as hyperthyroidism, hypothyroidism, goiter, and thyroiditis. There is also a small but serious risk of immune thrombocytopenia (ITP) that can occur post-alemtuzumab administration. Lastly, glomerulonephritis and single cases of autoimmune neutropenia, hemolytic anemia, and type 1 diabetes have been reported.[100] Therefore, extensive monitoring and early intervention allow for appropriate risk management.

Ofatumumab (Kesimpta)

Ofatumumab is a recombinant human monoclonal immunoglobulin G1 antibody that binds to CD20 expressed B-cells resulting in antibody-dependent cellular cytolysis and complement-mediated lysis. It is indicated for the treatment of relapsing forms of MS, including CIS, RRMS, and active SPMS in adults. Ofatumumab is the only once weekly subcutaneous injection DMT intended for self-administration.

Clinical studies have shown that Ofatumumab results in a significantly lowered annualized relapse rate versus teriflunomide. It also reduces the risk of 3-month confirmed disability progression and the number of T1 Gd+ lesions and T2 lesions. These effects were also seen in subgroup analyses defined by sex, age, body weight, prior nonsteroid MS therapy, and baseline disability and disease activity.[102,103]

The initial dose is 20 mg given at weeks 0, 1, and 2, followed by 20 mg given once a month starting at week 4. Ofatumumab should be given subcutaneously in the abdomen, thigh, or outer upper arm, avoiding any moles, scars, stretch marks, or other irritated or tender skin. The first injection should be administered under the supervision of a healthcare professional. It is available as a Sensoready® pen and prefilled syringes, which are onetime use only. These preparations should be stored in the refrigerator and allowed to reach room temperature for about 15 to 30 minutes prior to administration.

Prior to the first dose, hepatitis B screening and serum immunoglobulins should be performed, as well as the administration of all live or live-attenuated vaccines. The most common adverse medication reactions include upper respiratory tract infection and headache. Other warnings include increased risk of infections (including PML), injection-related reactions, reduction in immunoglobulins, and fetal risk. For these reasons, ofatumumab has a Medication Guide.

Mitoxantrone (Novantrone)

Mitoxantrone, a member of the anthracenedione family, is approved by the FDA for reducing neurologic disability and the frequency of clinical

relapses in patients with SPMS (chronic) or worsening RRMS.[104] Based on the clinical trials to date, the best MRI outcomes were seen in relapsing patients.[105] Additionally, clinical trials specifically documenting its effects on slowing MS progression in patients with SPMS have not been done.[104,105] Thus, support for the use of mitoxantrone in this context is lacking.[106]

Mitoxantrone is administered as a brief (5- to 15-minute) IV infusion dosed at 12 mg/m^2 every 3 months with a maximum allowable lifetime cumulative dose of 140 mg/m^2. Evaluations of left ventricular ejection fraction and ECG are required prior to each dose, and if signs or symptoms of congestive heart failure develop, they should be reexamined. Other potential adverse medication reactions include nausea, alopecia, menstrual disorder, amenorrhea, upper respiratory tract infection, UTIs, and leukemia. Mitoxantrone's role in the treatment of MS remains unclear due to the cardiac toxicity that limits its long-term use. More recent estimates also suggest the risk of leukemia may be as high as 1 in 145 patients, which has significantly decreased interest in its use for MS patients.[106]

Rituximab (Rituxan) and Ocrelizumab (Ocrevus)

Pharmacologically rituximab is a chimeric monoclonal antibody that targets the CD20 antigen on B cells. It is currently not FDA-approved for the treatment of RRMS and PPMS, but is often used off-label for this indication. In one retrospective observational study, its use demonstrated decreased in annualized relapse rate in RRMS and PPMS patients, while the EDSS remained unchanged.[107] Therefore, patients with PPMS who are less than 51 years old and have at least one gadolinium-enhancing lesion may benefit from rituximab therapy when given an infusion twice yearly.[107] The most common adverse reactions seen in this study were mild infusion-related reactions.

Ocrelizumab is a humanized version of the rituximab monoclonal antibody, and theoretically, it has lower autoantibodies formation and infusion reactions than its chimeric counterpart. Its mechanism of action is unknown but is presumed to involve CD20 binding, a cell surface antigen present on pre-B and mature B lymphocytes. Blocking CD20 effectively suppresses immune responses through depletion of CD20-expressing B cells.[39] It is the first medication FDA-approved for PPMS, and relapsing forms of MS.

Ocrelizumab has been associated with lower rates of disease activity and progression compared to interferon β_{1a} over the period of 96 weeks.[108] Its efficacy in PPMS patients was shown by approximately an 18% to 25% risk reduction in all study endpoints (ie, confirmed disability progression, timed 25-ft walk test [~7.5 m] performance, total volume of T2-weighted lesion, and decreased change in brain volume).[39]

Ocrelizumab's adverse events included infusion reactions necessitating subsequent dosing reductions, upper respiratory tract infections, and oral herpes activation. Neoplasms were also more common in the ocrelizumab group than placebo, with four patients receiving ocrelizumab developing breast cancer and three with basal cell carcinoma. Cervical adenocarcinoma in situ and basal cell carcinoma were the two neoplasms seen in the placebo group. This imbalance warrants ongoing evaluation in the context of the epidemiology of neoplasms in the MS population and the long-term experience with this and other CD20 treatments.[39] There have been a handful of cases with patients developing PML on ocrelizumab, but since all had natalizumab as prior therapy, they are considered carryover cases. In 2019, there was one case of a 78-year-old patient who developed PML on ocrelizumab and no prior DMT therapy, but other risk factors likely played a role in increasing this patient's risk. Regardless, monitoring for PML in all patients is recommended.

Ocrelizumab is given as a two-dose series via peripheral infusion, beginning with 300 mg given on day one and followed by another 300 mg on day 14. Subsequent doses of 600 mg are then given in 6-month intervals. Infusion rates are started at 30 mL/hr (for 300 mg in 250-mL bag starting doses) or 40 mL/hr (for 600 mg in 500-mL bag maintenance dose), which is stepped up based on patient tolerance, similar to rituximab. Monitor for infusion reactions throughout and up to 1 hour after infusion completion. The maximum infusion rate for the 300 mg is 180 mL/hr and 200 mL/hr for the 600-mg dose. Before ocrelizumab treatment starts, patients should be screened for hepatitis B, and for active infections before each infusion.[109]

Remaining Questions for Disease-Modifying Therapy

9 Despite the results from well-conducted clinical trials, several relevant treatment issues remain including; (1) when to begin therapy, (2) which agent to initiate, and (3) when to switch and stop therapies. The AAN has developed evidence-based guidelines regarding DMT use in MS. Key recommendations regarding initiating, switching, and stopping DMTs are summarized in Table 74-3.[55,110]

Decisions about medication use for MS include determining the illness severity, medication efficacy and adverse medication effect risks, and costs related to the therapy. These medications slow the course of the illness but do not suppress it completely, and in some individuals, no apparent benefit is reported. The vast majority of untreated patients will have progressive disease over time, and even in acute lesions, there is significant axonal damage that is essentially irreversible. MRI data show that 80% to 90% of all new enhancing lesions are asymptomatic, suggesting that a "quiet" clinical course does not necessarily mean there is not an ongoing disease activity that ultimately will lead to cognitive deficits and progressive spastic paraparesis.

Very early therapy is effective. In patients with CIS and two or more T2 lesions on brain MRI (ie, at high risk for developing CDMS), placebo-controlled studies with all three of the IFN agents and glatiramer acetate have shown significant delay in a second attack and positive outcomes on a variety of MRI measures.[57,110] Currently, the FDA has approved IFN-β_{1b}, IFN-β_{1a} (Avonex), glatiramer acetate, and some of the newer DMTs for use in CIS patients with abnormal MRIs consistent with demyelination. The AAN and CMSC recommend that patients with relapsing disease should be initiated on an FDA-approved DMT as soon as possible following diagnosis.[55,56,110]

Which DMT to use in which patient is the second major issue as there has not been a single, randomized study comparing DMTs in similar patient populations at the same time.[112] In the case of the first-generation self-injectables (see Table 74-2), results from pivotal placebo-controlled trials were more similar than different, including a nearly identical one-third reduction in relapse rate for all four medications over 2 years. A small number of studies suggest that frequent administration of IFN at higher doses may be more efficacious than lower dose, less frequent administration.[113,114] Other studies argue against this,[111,115] and some note no outcome differences between standard and double dose IFN-β_{1b} and glatiramer acetate,[115,116] or between IFN-β_{1a} (Rebif) and glatiramer acetate.[117]

Further complicating this issue is our understanding of the clinical differences between IFN products and the development of neutralizing antibodies. Between 30% to 40% of patients receiving IFN-β_{1b} develop antibodies directed against the medication; however, the exacerbation rate in these patients was similar to that seen in placebo-treated patients.[118] Neutralizing antibodies can occur as early as 3 to 6 months into IFN-β_{1b} treatment and as late as 18 months, as this product is the most antigenic.[119] Additionally neutralizing antibodies were found in 22% of early trials with IFN-β_{1a} (Avonex), but later studies report an incidence of 2% to 5%. This difference may be due to a formulation change making the product less antigenic.[111,117] Percentages of antibody formation for Rebif (approximately 12%) are intermediate. They may occur in the first 9 to 15 months of treatment, similar to Avonex.[118,119] Approximately 6% of patients treated with natalizumab show neutralizing antibodies that seem to diminish efficacy.[74] The long-term clinical significance of these findings is not completely clear, although data confirms a negative relationship between neutralizing antibodies and relapses, MRI lesions, and disability progression.[119-122] It is unknown if these antibodies cross-react between products, the duration of time in which they can be detected, and the impact corticosteroids have on their formation. Consensus guidelines outline when to test for neutralizing antibodies, which assay to use, or what titer cutoff to apply to patients in clinical settings exist.[123]

8 DMTs have been used to treat MS for more than two decades; however, patients continue to have more relapses, MRI lesions, disabilities, and ongoing disease progression to SPMS.[124] Although there is no accepted definition of treatment inadequacy, the Canadian Multiple Sclerosis Research Council has suggested a relatively simple approach that incorporates the elements of relapse rate, new MRI lesions, and change on the EDSS.[125] First, if significant and persistent IFN antibodies develop, switching to a non-IFN antibody (glatiramer acetate, natalizumab, ocrelizumab, fingolimod, siponimod, ozanimod, ponesimod, teriflunomide, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, ofatumumab, mitoxantrone, or possibly rituximab[126]) is reasonable. A second option is the addition of an immunosuppressant, such as monthly methylprednisolone,[127] azathioprine, methotrexate, or mycophenolate. As noted earlier, natalizumab added to IFN-β_{1a} produces rare cases of PML, and should not be used clinically.

Interestingly, the addition of a statin, specifically atorvastatin, into a beta-interferon agent may worsen MS,[128] although more research is needed.

Symptomatic Management

10 Many MS symptoms either do not require pharmacologic management or are nonresponsive. This section addresses the primary symptoms for which pharmacologic management may be beneficial (Table 74-4).[33,129-132]

Gait Difficulties and Spasticity

Gait problems can be caused by spasticity, weakness, ataxia, defective proprioception, or a combination of these factors. Spasticity is commonly encountered and tends to affect the legs more markedly than the arms, which can result in falls. As spasticity often presents late in the disease, the increased muscle tone of a spastic limb often lends pseudo-strength to patients with underlying weakness. While spasticity is amenable to pharmacologic intervention, muscle relaxants must not decrease muscle tone to the extent that ambulation is hindered.[33,130] Baclofen (Lioresal), a short-acting γ-aminobutyric acid (GABA) analog, is the preferred agent for spasticity and is started at 10 mg three times daily which is then titrated upward to achieve the desired response. Most patients respond with dosages between 40 and 80 mg/day, although some require dosages higher than the maximum recommended daily dose of 80 mg.[33,130] Due to oral baclofen's relatively short duration of action, continuous intrathecal administration of Gablofen may be used for patients unable to tolerate or unresponsive to oral therapy. Baclofen should not be abruptly discontinued to avoid seizures.[130]

Another effective agent for spasticity is tizanidine (Zanaflex), a short-acting, α-adrenergic agonist that acts in the CNS by increasing the presynaptic inhibition of motor neurons. Its efficacy is comparable to baclofen.[116] Starting at a dosage of 4 mg at bedtime, slowly titrated up over 2 to 4 weeks based on clinical response. The effective dosages range from 2 to 36 mg/day. Sedation, dizziness, and dry mouth are commonly reported adverse effects, but hypotension, as well as rare but severe hepatotoxicity, can occur. Tizanidine can be added to baclofen in small dosages, sometimes resulting in smaller doses of each medication and better outcomes.

In patients unable to tolerate baclofen or tizanidine, diazepam (Valium; 2-10 mg/day), clonazepam (Klonopin; 1-3 mg/day), or dantrolene sodium (Dantrium; 100-400 mg/day) may be alternatives; however, they generally are less effective. Mild spasticity may respond to gabapentin (Neurontin; 1,800-3,600 mg/day) or tiagabine (Gabitril; 8-56 mg/day) may be useful but adverse medication reactions can prohibit their use. Pregabalin (Lyrica; 75-300 mg/day) has similar features as gabapentin but is approximately three times more potent and does not saturate the GI tract L-transporter system, so it may prove helpful in treating spasticity.

Botulinum toxin type A (Botox) is effective in alleviating spasticity.[33] The amount required to exert a pharmacological effect is often too excessive to use safely in the larger muscles; therefore, its use is best limited to smaller areas of focal muscle spasm.

An alternative approach for gait disruptions are K^+ channel blockers such as 4-aminopyridine (4-AP), which can potentiate synaptic transmission and increase muscle twitch tension. Similar to 4-AP, dalfampridine (Ampyra; 20 mg/day) can improve walking speed in patients with MS.[131,132,137,138] In other countries, dalfampridine is referred to as fampridine.[138] Common adverse medication reactions of dalfampridine include UTIs, insomnia, dizziness, headaches, and balance disorders. This agent is associated with the risk of seizures, particularly when the maximum dose of 10 mg twice daily is exceeded. It is contraindicated in patients with a seizure history, and an REMS program is used to manage these risks. It is essential to educate patients not to take products containing 4-AP with dalfampridine, as therapeutically, it is a comparable extended-release product, which also means the medication should not be chewed, crushed, or cut. If a dose is missed, patients should take it immediately, take their dose upon recognition and never double the dosage due to seizure risk.

Tremor

Cerebellar symptoms such as tremor can be troubling and difficult to control. Helpful medications include propranolol, primidone, and isoniazid.

Bowel and Bladder Symptoms

Incontinence, urgency, frequency, and nocturia, are indications of a hyperreflexic bladder (ie, inability to store urine) and are common complaints. A number of anticholinergic agents, including tricyclic antidepressants, are used to treat mild symptoms. Still, with all anticholinergic agents, great care must be used to avoid falls and decreased cognition. Antimuscarinic agents can also treat incontinence. In patients with significant sphincter detrusor dyssynergia, oral α-adrenergic blockers or intramuscular botulinum toxin type A may relax the internal sphincter (see Chapter 105, "Urinary Incontinence").

Intermittent self-catheterization and the Credé maneuver, with or without a concomitant anticholinergic agent, are recommended for large postvoid residual volumes (more than 100 mL) or when the urinary problem is hyporeflexic in nature (failure to empty). Cholinergic agents like bethanechol may also be used for a hyporeflexive bladder. Treatment is important as large post-void residual volumes increase UTI risk, and therefore, urinary acidifiers

such as vitamin C or antiseptics such as methenamine mandelate may be used to prevent infections. Antibiotics used for UTI prophylaxis include sulfamethoxazole/trimethoprim, cephalexin, cinoxacin, and nitrofurantoin.

Constipation is the most common bowel complaint seen in patients with MS, as many medications (eg, opioids, anticholinergics) and voluntary water restriction in those patients with urinary urgency and incontinence may contribute to its risk. Increases in dietary fiber and hydration may alleviate this problem, but laxatives or enemas may be necessary (see Chapter 36, "Chronic Heart Failure").

Major Depression

Depressive symptoms and major depressive disorder are common in patients with MS. The risk of suicide may be increased markedly.[137] Patients should be monitored closely for symptomatology and treated accordingly (see Chapter 88, "Depressive Disorders"). IFN products and natalizumab should be used cautiously in patients with significant depressive symptoms.

Sensory Symptoms

Numbness and paresthesia are frequent sensory complaints related to MS, but usually do not require treatment. However, some patients may develop acute or chronic pain syndromes[130] such as trigeminal neuralgia and painful dysesthesias, for which treatment is necessary (see Chapter 79, "Pain Management").

Sexual Dysfunction

Sexual dysfunction in both men and females is common and counseling should be offered to both partners. Phosphodiesterase inhibitors or Alprostadil, a prostaglandin E1, can be very effective for erectile dysfunction (see Chapter 103, "Erectile Dysfunction"). Sildenafil (Viagra) is currently being studied in females with MS and sexual dysfunction. Bupropion (Wellbutrin) is the preferable antidepressant in patients for whom sexual dysfunction is a concern, due to its lower incidence of sexual adverse medication reactions.

Fatigue

Fatigue, a common complaint in MS patients, can be severely disabling, but often overlooked. Typically, it presents in the mid-to-late afternoon and can increase with heat exposure, exertion, concurrent infection, spasticity, weakness, and depression. Amantadine hydrochloride (100 mg twice daily) may offer significant relief.[33,129] Methylphenidate (Ritalin), dextroamphetamine (Dexedrine, Adderall), and related products are used commonly. Modafinil (Provigil), 200 to 400 mg daily, may be helpful for MS-related fatigue. Its *R*-enantiomer, armodafinil (Nuvigil), is dosed at 150 mg or 250 mg daily, reaches peak concentrations more quickly, and has potentially fewer adverse medication reactions than modafinil. In patients suffering from both depressive symptoms and fatigue, a more activating antidepressant such as fluoxetine may be employed.

Cognition

Cognitive dysfunction affects up to 50% or more of patients and manifests itself as word-finding difficulties and problems with concentration and short-term memory. Carefully review the patient's current medications before adding pharmacotherapy for cognitive dysfunction, as there are reports that statins and long-term proton-pump inhibitors can cause memory concerns. Cognitive dysfunction can be treated with stimulants or cholinesterase inhibitors if appropriate.

Pseudobulbar Palsy

Pseudobulbar palsy is a condition caused by progressive degeneration of the corticobulbar tract in patients with MS. Symptoms include dysarthria, dysphonia, dysphagia, and sudden, inappropriate, uncontrollable, emotional outbursts such as crying or laughing. A combination product of dextromethorphan and quinidine 20 mg/10 mg (Nuedexta) is used for its treatment; however, its mechanism of action is unknown. It is dosed as one capsule daily for 1 week, followed by one capsule twice daily. The quinidine included in this product inhibits the CYP2D6 enzyme leading to an increased dextromethorphan serum concentrations.

Complementary and Alternative Therapies for MS

Approximately 33% to 80% of patients with MS use complementary and alternative medicine (CAM) therapies.[133] These include the use of diet and dietary supplements such as vitamins, minerals, and herbs. Antioxidant supplements vitamin A, C, E, α-lipoic acid, coenzyme Q10, grape seed, pine bark extracts, mangosteen, and acai have suggestive benefits. However, for patients with MS, the antioxidant supplements hold a theoretical risk given their ability to stimulate the immune system (T cells and macrophages). Thus, their use may worsen or exacerbate their disease by counteracting the effects of immunomodulators. Other immune-stimulating supplements such as garlic, ginseng (Asian and Siberian), Echinacea, cat's claw, astragalus, alfalfa, and stinging nettle should be used with caution.[134]

Table 74-5 outlines updated AAN evidence-based CAM recommendations in MS.[133] The safety of these therapies when used in combination with DMTs has not been studied. Nor has information about medication interactions, however, healthcare providers can provide objective information regarding CAM use in MS and can assist their patients in making decisions.[122] A few of the CAM therapies listed below have been given Level A recommendations, meaning their use has been established but for most a Level B recommendation has been given, meaning they are probably effective.[122]

Vaccine Recommendations

Avoid live vaccine administration in any patients with MS receiving DMTs due to immunosuppression and the potential for the live virus vaccines to increase MS disease activity. Vaccines considered safe include the human papillomavirus, tetanus, rabies, and inactivated polio.[56] A yearly flu shot is recommended for all patients with MS, including those receiving any DMTs, while the intranasal influenza vaccine FluMist, a live-attenuated vaccine, is not. It is unknown if the intranasal influenza vaccine directly interacts with DMTs.[132] An exception to this rule applies to patients taking fingolimod, and alemtuzumab, who are negative for varicella-zoster antibodies. They should receive the non-live virus immunization at least 2 months before beginning treatment to allow time to mount an antibody response prior to immunosuppression. For unvaccinated patients at high risk for hepatitis B exposure, this vaccine should be given prior to ocrelizumab doses. This vaccine is not necessary for patients at low risk for exposure.[56]

EVALUATION OF THERAPEUTIC OUTCOMES

For those with acute MS exacerbations, treatment response is commonly seen within days. However, the clinician and patient should recognize that short-term (days to weeks), little or no apparent benefit may be noted when using a DMT. Therefore, therapeutic outcome evaluation is conducted over months to years by monitoring MS exacerbations, hospitalizations, disease progression, and disability measured using scales such as EDSS. Patients should be given realistic goals and treatment expectations to maximize medication adherence, in addition to being fully counseled regarding adverse effects. They should also be encouraged to participate in the evaluation of therapeutic response and actively encouraged to adhere to their prescribed regimens. If nonadherence is suspected, an investigation into barriers, such as injection fatigue or intolerable adverse medication reactions, should be done. Discussion around medication cost and/or switching agents to one that may provide increased adherence should also be done.

Each DMTs has specific safety monitoring recommendations to follow. Specific safety monitoring parameters for the newer DMTs can be found in Table 74-2. In general, patients on any DMT should receive regular laboratory monitoring and close observation, including regular neurologic examinations, frequent evaluation for adverse effects, and/or changes in disability. Natalizumab and alemtuzumab have REMS programs, and fingolimod, siponimod, ozanimod, ponesimod, and cladribine have Medication Guides to monitor safety. Healthcare providers should follow the requirements of these programs. Laboratory monitoring for IFN therapy should include a CBC, platelet count, and LFTs completed at baseline, every 3 months for 1 year, and every 6 months after that. However, glatiramer acetate requires no specific laboratory monitoring. Teriflunomide requires a transaminase, bilirubin, CBC, tuberculin skin test, and blood pressure before therapy is started. Additionally, alanine aminotransferase should be monitored every 6 months after starting treatment. Patients on teriflunomide should be evaluated for renal failure and increased serum potassium as needed. Dimethyl fumarate requires a CBC prior to beginning therapy, within 6 months after treatment initiation, followed by annually. During these times, LFTs should also be monitored for patients on dimethyl fumarate.

CONCLUSION

The diagnosis and treatment of MS can be difficult, and until recently, treatment was particular to the MS center or treating neurologist. The AAN has the most updated guidelines for DMTs for adults with multiple sclerosis.[55] These focus on shared patient-centered decision making, where the patient is given general information about dosing schedule, route of administration, and adverse medication reactions for their specific disease presentation.

The team works with the patient to make treatment decisions on how to best help the patient manage their illness, working to improve primary, secondary, and tertiary disease outcomes. More aggressive treatment with alemtuzumab, fingolimod, or natalizumab is required for people with highly active MS, and with ocrelizumab for patients with PPMS where the benefits outweigh the risks.[55] The most severe adverse effect associated with MS treatments is PML, and guidelines for natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate specifically note that patients should be counseled on this adverse effect. By moving to a patient-centered MS care approach, disease outcomes (due to increased adherence) and treatment satisfaction should improve as it is only through collaboration as a care team that we will be able to combat this debilitating disease.

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ABBREVIATIONS

AAN	American Academy of Neurology
ACTH	adrenocorticotropic hormone
ADCC	antibody-dependent cell-mediated cytolysis
4-AP	4-aminopyridine
BCRP	breast cancer-resistant protein
CAM	complementary and alternative medicine
CBC	complete blood count
CDMS	clinically definite multiple sclerosis
CIS	clinically isolated syndrome
CNS	central nervous system
CSF	cerebrospinal fluid
DMT	disease-modifying therapy
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
ECG	electrocardiogram
EDSS	expanded disability status scale
GI	gastrointestinal
HLA	human leukocyte antigen
IAR	infusion-associated reaction

IFN	interferon
IgG	immunoglobulin G
IL	interleukin
INR	international normalized ratio
IRIS	immune reconstitution inflammatory syndrome
ITP	immune thrombocytopenia
IV	intravenous
JCV	John Cunningham virus
LFT	liver function test
MBP	myelin basic protein
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
PEG	polyethylene glycol
PLEX	plasma exchange
PML	progressive multifocal leukoencephalopathy
PPMS	primary-progressive multiple sclerosis
PRMS	progressive-relapsing multiple sclerosis
REMS	Risk Evaluation and Mitigation Strategy
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary-progressive multiple sclerosis
TGF	transforming growth factor
Th	T-helper cells
THC	tetrahydrocannabinol
Treg	T-regulatory cells

UTI	urinary tract infection
VCA	vascular cell adhesion
VCAM	vascular cell adhesion molecule
VEP	visual-evoked potential
VLA-1	very-late antigen 1

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SELF-ASSESSMENT QUESTIONS

1. At the time of diagnosis, which of the following forms of multiple sclerosis (MS) is the *most* common?
   A. Primary-progressive
   B. Relapsing-progressive
   C. Relapsing-remitting
   D. Secondary-progressive
2. When initiating natalizumab therapy 300 mg IV every four weeks, which of the following is *not* a monitoring parameter?
   A. Liver function tests
   B. Anti-JCV antibodies
   C. Tuberculin skin test
   D. MRI
3. Which of the following is used in the treatment of an exacerbation (attack/relapse) of MS?
   A. Oral immunoglobulin
   B. High-dose IV methylprednisolone
   C. Low-dose oral prednisone
   D. Dalfampridine
4. PJ is a 47-year-old female with RRMS who presents to the clinic with complaints of fatigue. The physician decides to prescribe a medication for the symptomatic treatment of fatigue. Which of the following agents would *not* be appropriate?
   A. Methylphenidate 5 mg every morning
   B. Modafinil 200 mg every morning
   C. Amantadine 100 mg twice daily
   D. Dextromethorphan/quinidine 20 mg / 10 mg every morning
5. Which is *true* about spasticity in MS?
   A. Spasticity occurs early after a patient is diagnosed with MS
   B. Increased muscle tone due to spasticity in late-stage MS can help to decrease falls due to weakness
   C. Fluoxetine is a first-line agent to treat spasticity
   D. Baclofen is useful orally, intrathecally, and IV for spasticity

6. When counseling a patient about interferon therapy for MS, you should communicate to the patient which important aspect regarding efficacy?

   A. They will start to notice a change in symptoms immediately.

   B. They must freeze the medication.

   C. It may take up to one or two years to see a change on the MRI.

   D. The medication works best if a double dose is given.

7. Interferon-β_{1a} (Rebif) differs from Interferon-β_{1a} (Avonex) in what way?

   A. Rebif is given once per week.

   B. Rebif is given as an intramuscular injection.

   C. Rebif is given three times per week.

   D. Rebif causes tissue necrosis.

8. SW is a 72-year-old male currently on Interferon-β_{1a} (Rebif) 44 mcg subcutaneously three times per week, warfarin, and amiodarone. In the past six months, he has had three exacerbations and multiple new enhancing lesions on MRI. Following the discontinuation of Rebif what is the best next step in his course of therapy?

   A. Natalizumab

   B. Glatiramer acetate

   C. Mitoxantrone

   D. Fingolimod

9. Which of the following is *not* a side effect seen with Sphingosine-1 phosphate receptor modulators (fingolimod, siponimod, ozanimod, ponesimod)?

   A. Bradycardia

   B. Depression

   C. Infection

   D. Increased Liver Enzymes

10. SC, a 30-year-old female, was prescribed teriflunomide 7 mg orally daily for the treatment of her relapsing MS. Which of the following counseling points is *false*?

    A. Teriflunomide is a pregnancy category X medication and a contraceptive method is recommended.

    B. Alopecia, nausea, headache, and paresthesias are common side effects associated with teriflunomide.

    C. A cholestyramine washout may be considered if pregnancy is desired.

    D. Teriflunomide causes secondary leukemia in 1 in 1,400 patients.

11. Efficacy of the ocrelizumab can be attributed to which mechanism of action?

    A. Depletion of CD20 expressed B-cells

B. α_1- and β_1-blockade

C. Sphingosine-1-phosphate receptor modulation

D. Blockade of t-lymphocyte migration into CNS

12. Diroximel fumarate (Vumerity) is thought to act by which of the following mechanisms of action?

A. Decrease matrix metalloproteinases

B. Inhibition of the proliferation of reactive T cells

C. Decreased number of adhesion molecules

D. Activation of Nrf2 pathway

13. MB, a 35-year-old female with RRMS, asks you about an MS drug that requires a 6-hour observation period. Which of the following drugs requires a 6-hour observation monitoring period?

A. Ocrelizumab

B. Natalizumab

C. Fingolimod

D. Ponesimod

14. CC, a 52-year-old female, is having difficulty walking without stopping every 25 ft (~7.5 m) or so to take a break. Which of the following drugs is the most appropriate choice for CC at this time?

A. Ozanimod

B. Modafinil

C. Interferon-β_{1a} (Extavia)

D. Dalfampridine

15. Which agent is contraindicated in pregnancy?

A. Siponimod

B. Teriflunomide

C. Monomethyl fumarate

D. Natalizumab

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** RRMS is the most common form of diagnosed MS, which accounts for about 85% of patients.

2. **C.** A tuberculin skin test is only indicated with the use of teriflunomide and alemtuzumab (Table 74-5).

3. **B.** High-dose methylprednisolone is used first-line to treat acute relapses/exacerbations.

4. **D.** Dextromethorphan/quinidine 20 mg / 10 mg is used to treat pseudobulbar affect, not fatigue.

5. **B.** Increased muscle tone lends to pseudo-strength with underlying weakness. Spasticity usually occurs late in the disease process. Fluoxetine is best used for fatigue if a patient is also depressed due to its activating mechanism. Baclofen is not used IV, only oral and intrathecally.

6. **C.** Immediate changes in symptoms are not noted with interferon therapy, and it can take up to 1 to 2 years to see a change on MRI. Never double the dose of the medication, and the medication should not be frozen.

7. **C.** Avonex is given IM one time weekly, while Rebif is given by subcutaneous injection three times weekly. Their side effect profiles are similar but may be less frequent with Avonex due to less frequent injections (Table 74-3).

8. **A.** Natalizumab is the most effective DMT available, and due to the patient having multiple relapses/exacerbations, multiple new MRI lesions, and his older age, it is best to give a more aggressive treatment since the disease is progressing quickly. Fingolimod is not as effective as natalizumab, and the patient is on amiodarone, which is contraindicated with fingolimod therapy due to bradycardia and heart block. Glatiramer acetate would give no increased benefit compared to interferon therapy in the patient.

9. **C.** Depression is a side effect for interferon therapies and not S1P receptor modulators (Table 74-5).

10. **D.** Teriflunomide use is not associated with secondary leukemia, but mitoxantrone is associated with this adverse effect.

11. **D.** The mechanism of action of ocrelizumab causes antibody-dependent cytotoxicity through selectively binding B-cells with CD20.

12. **D.** Although the exact mechanism of action of diroximel fumarate is unknown, it is thought to be due to anti-inflammatory and cytoprotective properties via activation of the Nrf2 pathway.

13. **C.** Fingolimod has a 6-hour first-dose observation period due to risk of bradycardia. Siponimod and ozanimod carry a warning and only require the 6-hour observation period for patients with high risk for bradycardia. Ponesimod only requires a 4-hour observation for certain patient populations.

14. **D.** Dalfampridine is specifically used to increase walking speed.

15. **B.** Teriflunomide is contraindicated in pregnancy, and an accelerated elimination procedure is put in place to clear the drug if needed for contraception for both females and males.