New Therapeutic Options for Multiple Sclerosis: An Update for Specialty and Managed Care Pharmacy

Educational Objectives

1. Describe the pathophysiology and disease characteristic/types of multiple sclerosis (MS);
2. Identify medications that are U.S. Food and Drug Administration (FDA)-approved for the treatment of all types of MS;
3. Discuss basic characteristics of currently available MS medications, including mechanism of action, dosage and administration, adverse effects, and drug interactions;
4. Describe the relationship between medication adherence and MS disease control and potential strategies for overcoming barriers to adherence; and
5. Describe the approval pathway for current and future non-innovator MS medications and discuss methods to counsel patients about disease management.

Post-test/Rationale

1. The most common presentation of multiple sclerosis (MS) is:
   A. Relapsing-remitting MS (RRMS)***
   B. Secondary-progressive MS (SPMS)
   C. Primary-progressive MS (PPMS)
   D. Progressive-relapsing MS (PRMS)

Correct Answer: A

The most common type of MS, affecting 85% of patients, is known as relapsing-remitting MS (RRMS).

2. Symptoms of MS include all of the following except:
   A. Cognitive disturbances
   B. Dyspnea***
   C. Muscle spasticity
   D. Fatigue
Correct Answer: B

Disease presentation is variable and characterized by nonspecific symptoms, including optic neuritis or other visual symptoms, gait problems, muscle spasticity or weakness, speech, or cognitive changes, bladder or bowel dysfunction, or fatigue.

3. Which of the following new MS medications is approved for relapsing forms of multiple sclerosis?

A. Dimethyl fumarate (Tecfidera)
B. Fingolimod (Gilenya)
C. Peginterferon beta-1a (Plegridy)
D. All of the above***

Correct Answer: D

Interferon beta and glatiramer acetate are considered first-line disease modifying agents for the treatment of RRMS. Interferon beta, a first-line treatment for MS, is available in the following 5 formulations: Avonex (beta-1a, intramuscular injection given once a week), Rebif (beta-1a, subcutaneous injection given 3 times a week), Plegridy (beta-1a, subcutaneous injection q 14 days), and Betaseron and Extavia (beta-1b, subcutaneous injection given every other day). Fingolimod (Gilenya) was the first oral drug for the treatment of MS to come to market in 2010, indicated for relapsing forms of MS. Dimethyl fumarate (Tecfidera) is an orally-administered immunomodulatory agent shown to induce T-helper 2-like cytokines (including interleukins 4, 5, and 10) to cause apoptosis in activated T cells. It also causes down regulation of intracellular adhesion molecules, leading to reduced migration of lymphocytes. It is approved to treat relapsing forms of MS.

4. JP is a 25yo female of Northern European descent presenting with worsening of her pre-existing difficulty walking and fatigue. She also has new-onset loss weakness in her left lower extremity that has been present for 4 days with no fever. Which of the following would you use to treat JP's acute exacerbation of MS?

A. Interferon beta (Avonex)
B. Methylprednisolone (Solu-Medrol)***
C. Fingolimod (Gilenya)
D. Natalizumab (Tysabri)
Correct Answer: B

Relapses or exacerbations are managed by steroids. Corticosteroids decrease inflammation by suppressing migration of polymorphonuclear leukocytes and reversing capillary permeability. Methylprednisolone (Solumedrol) is given as 1 gram IV for 3-5 days and may or may not be followed by a prednisone taper.

5. Which is true of fingolimod (Gilenya)?

A. Blocks pyrimidine synthesis in rapidly dividing cells through inhibition of mitochondrial dihydroorotate dehydrogenase, inhibits protein tyrosine-kinase and cyclo-oxygenase-2 activity, and decreases the ability of antigen presenting cells to activate T-cells.
B. Sequesters lymphocytes in lymphatic system, decreasing the overall number of lymphocytes in circulation***
C. Intercalates with DNA strands, causing breaks, and inhibits DNA repair through topoisomerase II
D. Inhibits α4-mediated adhesion to leukocytes to their counter-receptors(s) and prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue

Correct Answer: B

Fingolimod is phosphorylated to its active form, FTY720-P, and binds to sphingosine-1-phosphate (S1P) receptors S1P1 and S1P3-5 on the surface of lymphocytes. It thereby depletes both CD4+ and CD8+ T lymphocytes in the blood stream, up to 75% below baseline. CD4+ cells are decreased to a greater extent than CD8+ cells. It also inhibits lymphocyte release from lymphatic organs decreasing overall numbers in circulation.

6. TD is a woman 18 years of age that was recently diagnosed with RRMS. She is very concerned about using injectable medications and questions you about possible oral treatment options. Which of the following MS medications are available in an oral formulation:

A. Dimethyl fumarate (Tecfidera)***
B. Natalizumab (Tysabri)
C. Glatiramer acetate (Copaxone)
D. Mitoxantrone (Novantrone)
Fingolimod (Gilenya) was the first oral drug for the treatment of MS to come to market in 2010 indicated for relapsing forms of MS. Prior to 2010 there were 6 medications approved for the treatment of RRMS. These included interferon beta, glatiramer acetate, natalizumab, and mitoxantrone. All of these medications had to be given parenterally, by injection or infusion, and compliance may have been an issue for patients, particularly as patients developed injection fatigue. In 2010, fingolimod entered the market as the first oral agent and was soon followed by teriflunomide and dimethyl fumarate.

7. Which of the following medications can be used to improve difficulty walking:
   A. Dalfampridine (Ampyra) ***
   B. Phenytoin (Dilantin)
   C. Oxybutynin (Ditropan)
   D. Methylphenidate (Ritalin)

Correct Answer: A

Dalfampridine (Ampyra) is the only medication to be specifically approved for a specific symptom of MS, to improve walking.

8. Adherence has been shown to reduce all of the following except:
   A. Relapses
   B. Hospital visits
   C. Hospital admissions
   D. Adverse effects***

Correct Answer: D

Adherence has been linked with improved outcomes in patients with MS, including fewer relapses, hospital visits, and hospital admissions.
9. All of the following are barriers to adherence EXCEPT:

A. Side effects  
B. Patient assistance programs***  
C. Frequency of administration  
D. Cost  

Correct Answer: B

Factors affecting patient reported nonadherence include the following: forgetting to administer medications, injection site reactions, injection fatigue, side effects, frequency of administration, cognition and complexity of regimen, monitoring requirements, presence of active disease symptoms, patient self-efficacy, patient-clinician relationships, quality of life, patient perception of the injectable medication, hope, depression, and degree of support. Cost may be another major barrier to adherence, with an average cost per prescription for MS medications being approximately $4500. Strategies to minimize barriers to adherence can include adherence aids, education support groups, choosing a medication based on patient-specific factors, and using medications in a formulation that can increase a patient’s comfort level, as well as using medications available in prefilled syringes, auto-injectors, or pens, which may increase a patient’s comfort level with an injectable medication. It is important to educate patients and providers about patient assistance programs as well.

10. According to the FDA, which of the following aspects of active ingredient sameness has Glatopa demonstrated in comparison with the referenced listed drug/innovator product Copaxone:

A. Equivalent fundamental reaction scheme  
B. Equivalent physicochemical properties including composition  
C. Equivalent structural signatures for polymerization and depolymerization  
D. All of the above***  

Correct Answer: D

The FDA thoroughly evaluated active ingredient sameness and performed its own analytical testing before determining the equivalence of these 2 products. Glatopa was determined to have equivalent fundamental reaction scheme, equivalent physicochemical properties, including composition, and equivalent structural signatures for polymerization and depolymerization.