MULTIPLE SCLEROSIS DRUG REVIEW

ACTIVITY DESCRIPTION
Multiple sclerosis (MS) patients use a variety of medicinal agents for disease modification, symptom control and their resulting side effects. Disease-modifying therapies (DMTs) use daily, every other day, thrice weekly and once weekly subcutaneous, intramuscular injection, and most recently approved oral dosage schedules. This article will review the individual DMTs for MS along with common medications used specifically for symptom control.

TARGET AUDIENCE
The target audience for this activity is pharmacists and pharmacy technicians in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:

- List medicinal names and routes of administration for the Disease-modifying Therapies for Multiple Sclerosis
- Understand and describe storage requirements for Multiple Sclerosis therapies
- Understand mechanisms of actions and list common and severe adverse events
- Describe common Multiple Sclerosis-associated disorders and be able to list potential pharmacologic and non-pharmacologic methods of treatment

After completing this activity, the pharmacy technician will be able to:

- List drugs used to treat multiple sclerosis
- List routes of administration of these drugs

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Universal Activity No.: 0798-0000-14-091-H01-P&T
Credits: 3 contact hours (0.3 CEU)

Release Date: May 28, 2014
Expiration Date: May 28, 2016

ACTIVITY TYPE
Knowledge-Based Home Study Monograph

FINANCIAL SUPPORT BY
PharmCon, Inc.
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Multiple sclerosis (MS) patients use a variety of medicinal agents for disease modification, symptom control and their resulting side effects. Disease-modifying therapies (DMTs) use daily, every other day, thrice weekly and once weekly subcutaneous, intramuscular injection, and most recently approved oral dosage schedules. The clinical benefits of DMTs appear to be more effective with early, aggressive treatment.\textsuperscript{1,2,3} Relapse rates while using DMTs are modestly reduced. On the other hand, compliance rates are substantially affected with injectables due to both the side effect profiles and injection type phobias, giving the oral preparations an advantage as patients gravitate towards a less invasive alternative.\textsuperscript{1} In 2010, an oral preparation of fingolimod was FDA approved for the treatment of MS, giving patients a much needed option.\textsuperscript{4} Since then, two other oral preparations, teraflunomide and dimethyl fumarate, have been approved thereby propelling the orally approved medications into the limelight.\textsuperscript{5,6} While combating relapse rates and gadolinium enhancing lesions, patients are also treated symptomatically for issues ranging from neurogenic bladder and cognitive dysfunction to spasticity and fatigue.\textsuperscript{7} This article will review the individual DMTs for MS along with common medications used specifically for symptom control.

**Disease-Modifying Therapies Used in Multiple Sclerosis**

The discovery of interferon therapy in the 1990s improved survival rates, slowed disease progression and improved quality of life (QoL) for patients suffering from MS. Betaseron\textsuperscript{®} approval in 1993 was subsequently followed by Avonex\textsuperscript{®}, Rebif\textsuperscript{®}, Copaxone\textsuperscript{®}, Novantrone\textsuperscript{®} and Tysabri\textsuperscript{®}.\textsuperscript{1} Injectable routes of administration had been the only available option for MS treatment until fingolimod (Gilenya\textsuperscript{®}) approval in 2010 and followed by teraflunomide (Aubagio\textsuperscript{®})(2012) and dimethyl fumarate (Tecfidera\textsuperscript{®})(2013).\textsuperscript{5,6} Conflicting evidence regarding efficacy between the available DMTs has been reported. Some sources suggest early, higher dosage forms, and more frequent dosing regimens offer better clinical efficacy while others suggest the route of administration offers no particular advantage.\textsuperscript{3,8} Moreover, long-term studies over 4 to 5 years are scarce and thought to be unethical, making long-term
disability projections of DMTs difficult.\textsuperscript{2,9-11} However, consistent data suggest an early, dose dependent response helps to decrease the frequency and severity of relapses in addition to delaying disease progression in relapsing-remitting MS (RRMS) which is the long-term goal for MS patients.\textsuperscript{1,3,8,9}

Categorized into four different types of MS, most medications approved are usually for RRMS. Approximately 85% of patients present with the RRMS type while others may experience secondary-progressive (SPMS), primary-progressive (PPMS) or progressive-relapsing (PRMS).\textsuperscript{12,13} Epidemiologic studies identify an increased incidence of MS in people living in high latitudes (areas further away from the equator), women, Caucasians, in those contracting certain infectious agents, and patients with other autoimmune disorders. Additionally, genetic studies have reported an increased prevalence of MS (10% to 15%) in people with an affected family member.\textsuperscript{13}

The most prevalent form of MS (RRMS) consists of abrupt episodes of disease activity lasting several weeks followed by complete or partial recovery. Reports have shown that as much as 50% of people presenting with RRMS will develop SPMS within 10 years. SPMS involves a gradual progression of disability with or without relapses while the other two forms of MS involve progression of disability from the onset of the disease. People with PPMS show no signs of relapses while PRMS patients display superimposed relapses.\textsuperscript{12,13}

\textbf{Interferon Therapy}

Interferons are proteins naturally produced in the human body in response to viral infections. Type I (alpha, beta, tau and omega) and type II (gamma) interferons combat viral infections through a series of actions that lead to alterations in the immune cellular effects of cytokines. Consequently, trials were undertaken studying the effects of interferon therapy versus MS-associated viruses. As a result, only type I interferons were determined to be beneficial in MS.\textsuperscript{13} Interferons theoretically work by T cell inhibition, reduction in matrix metalloproteinases and pro-inflammatory cytokines along with increasing
anti-inflammatory cytokines. While conflicting studies exist as to equivalence between the dosage forms, all available preparations have proven efficacy in MS and have become a mainstay in MS treatment since their introduction in 1993.\textsuperscript{13-15} However, an important topic of concern seen with all MS interferon injectable medications, rendering numerous articles and debates, is the neutralizing antibody (NAb). Prevalent in varying degrees depending upon the interferon used, conflicting evidence abounds with several clinical trials suggesting a reduction in efficacy and an increase in disease activity especially in patients with a high titer of NAbs.\textsuperscript{16-21} A comparison of interferon preparations report intramuscular injections (IM) have shown decreased incidence of NAbs versus subcutaneous injections. Clinical research suggests increased clearance from the injected muscle as the possible cause.\textsuperscript{14,16,18} Even with data suggesting subcutaneous injections increase the probability of Nabs and a possible decrease in effectiveness, there is currently insufficient data in the United States allowing neurology experts to render an opinion. A change of medication is only suggested if the patient is not faring well on currently prescribed interferon medication in addition to the presence of NAbs. Moreover, cross-reactivity is seen between the interferon medications in regards to NAbs, necessitating a switch to a different class of drug like glatiramer acetate or another DMT if warranted.\textsuperscript{19-21}

**Avonex\textsuperscript{®} (Interferon beta-1a)**

Avonex\textsuperscript{®} is a glycosylated interferon beta-1a recombinant DNA injectable that is produced in Chinese hamster ovary cells.\textsuperscript{13,22} While glycosylation effects in Avonex\textsuperscript{®} may not be fully known, it has been shown to affect stability, activity, half-life, and distribution in other proteins.\textsuperscript{22} Avonex\textsuperscript{®} is engineered to mimic the actions of naturally occurring human interferon beta proteins. It is indicated and FDA approved as an intramuscular injection (IM) given as a once weekly 30 μcg dose for RRMS.\textsuperscript{13,14,22} Avonex\textsuperscript{®} is preferred by some to confine the occurrence of side effects allowing for less time off from work while simultaneously reducing the number of injections over an indefinite period of time.\textsuperscript{22,23} Avonex\textsuperscript{®} reportedly decreases disease progression, physical disability and reduces the prevalence of
disease exacerbations in RRMS. Active lesions as seen on MRI are significantly reduced while disease progression is decreased by as much as 37%. Early treatment with Avonex® has been shown to decrease the rate of conversion to clinically definite MS (CDMS) by up to 44%, a 57% reduction in the quantity of new lesions seen on MRI as well as a 67% reduction in enhancing lesions.²

Patients may choose from a lyophilized powder vial for reconstitution, a prefilled syringe with or without the Avostartgrip®, and a single-use prefilled autoinjector pen. A titration regimen is recommended for all supplied Avonex® dosage forms. Additionally, an Avostartgrip® kit provides 3 titration devices. However, the kit may only be used with Avonex® pre-filled syringes. Storage and needle requirements vary (Table 1). Biogen Idec, the manufacturer of Avonex®, offers free training resources for the patient to include injection techniques as well as the availability of nurses to help answer any questions that may arise through their Avonex MS Active Source® program at 1-800-456-2255.²²-²⁴

Common among MS injectables, injection site reactions (ISRs) affect approximately 20% of patients and are experienced the least out of all the interferon DMTs. Additionally, ISRs do not decrease with continued use.¹,²²,²⁵ While subcutaneous injections have been studied in MS, intramuscular injection prolongs absorption, resulting in sustained serum levels with fewer ISRs.¹,²² Contraindications for using Avonex® include any experienced hypersensitivity reaction. However, patients allergic to albumin should avoid taking the lyophilized powder for reconstitution as it contains human albumin.²² One of the most common side effects is Flu-like symptoms (FLS) which typically decrease with continued use (Table 2).¹,¹³,²² However, FLS reportedly occur most frequently with Avonex.¹,²⁶ Hair loss, affecting up to 53% of interferon users, usually appears during the first 6 months of therapy.²⁶ Of special note, patients that become pregnant while taking Avonex® should be immediately referred to their doctor due to possible teratogenic effects. Laboratory monitoring
assessing complete blood cell counts (CBC) with differential, platelet counts, and liver function tests are recommended during use.  

**Betaseron®/Extavia® (Interferon beta-1b).**

Betaseron® was the first interferon introduced on the market in 1993 by Bayer® for RRMS. In 2009, Novartis® introduced an identical interferon beta-1b onto the market called Extavia®. Although the FDA lists both medications as having no therapeutic equivalents, both medications have been FDA approved for RRMS. According to a clinical pharmacology and biopharmaceutics review submitted to the Center for Drug Evaluation and Research in June 2009, Betaseron® and Extavia® are identical in structure and indication. Since the two medications are considered identical in structure, and for the sake of convenience, discussion regarding Betaseron® will also correlate to Extavia® except where noted.

Betaseron® is a recombinant DNA formulation manufactured in E. coli containing human interferon beta_{ser17}. However, it varies from the endogenous form as it only contains one amino acid substitution and is not glycosylated. An every other day subcutaneous injection schedule keeps biologic response at clinically effective levels. Being a Type I interferon, Betaseron®, as well as the other injectable interferons, is believed to lead to an expression of proteins such as neopterin, \( \beta_2 \) microglobulin, MxA and IL-10. While the exact mechanism of action (MOA) is unknown, it has been theorized that Betaseron® reduces antigen presentation, enhances suppressor T cells and anti-inflammatory cytokines (IL-10), inhibits lymphocyte recruitment into the CNS and helps maintain the blood brain barrier (BBB) integrity. Since the approval of Betaseron®, it has remained a first-line DMT in MS, displaying a 31% reduction in relapse rates and up to a 75% reduction in new lesions as seen on MRI.
Betaseron® and Extavia® come in lyophilized powder vials for reconstitution and are injected subcutaneously every-other-day. A 6-week titration schedule for both medications, consisting of a 25% dose for the first two weeks, 50% dose weeks 3 to 4, 75% dose weeks 5 to 6 with a full dose thereafter, is recommended to reduce side effects. Both medications may be refrigerated or stored at room temperature (Table 1). Each medication has a support program available for injection training, health-related questions, and insurance issues. The BETAPLUS® program may be reached 24/7 at 1-800-788-1467 while the EXTAVIA Go Program is available at 1-866-398-2842.²⁵,²⁹,³⁰

Adverse events are common with Betaseron® (Table 2).¹⁴,²⁵,²⁸,³¹ Approximately 57% and 78% of patients experience FLS and ISRs respectively.¹,¹⁴,²⁵ Injection site reactions and NAbs are most frequent with Betaseron® versus other interferons although proper injection technique reportedly reduces the probability of skin reactions.²³,²⁸,³¹ Rotation of injection sites is necessary to minimize ISR severity.¹⁴,²⁵,²⁸,³¹ In addition to FLS and ISRs, women are at risk for miscarriage and harmful fetal effects while taking Betaseron®. Discontinuation of use and an immediate call to their doctor is recommended if pregnancy occurs. Like lyophilized Avonex®, Betaseron® contains human blood based albumin which should not be used in people allergic to it. Furthermore, a rare risk of viral transmission such as Creutzfeldt-Jakob disease (CJD) may occur due to inclusion of human albumin.²⁵ Laboratory monitoring of CBCs with differential and hepatic function are recommended.¹⁴,²⁵

Rebif® (Interferon beta-1a).

Rebif®, an interferon beta-1a genetically engineered in Chinese Hamster Ovary (CHO) cells, is configured to have the exact same amino acid sequence of human interferon and is glycosylated. Rebif® was as either a 22 mcg or 44 mcg dose given three times weekly and indicated for RRMS to reduce the number of exacerbations and delay the progression of physical disability.³² Scientific studies abound showing significant clinical effects for both dosage strengths on reduction of attack rates (29% and 32%
respectively), Extended Disability Status Scores (EDSS), T2 disease burden as seen on MRI, and a delay in the development of CDMS by 24% in patients receiving the 22 mcg dosage if initiated early on after a patient experiences an isolated event (optic neuritis, spinal cord syndrome, or cerebellar syndrome).²,³² A 2-year study reviewing the effects of 22 mcg, 44 mcg doses of Rebif® versus placebo was followed by an extension study switching placebo patients over to either dosage forms of Rebif®. The extension study was to assess issues in the situation of delayed treatment. Moreover, patients were given an opportunity after completion of the initial study enrolled for a longer period of time whereby efficacy, tolerance and safety were observed, ending 8 years after their initial enrollment. The initial study reported a 78% reduction in MRI T2 active lesions, increased relapse times and a 26% reduction in disability progression in those using the 44 mcg thrice weekly regimen. Patients switched from placebo to either regimen displayed annualized relapse rates (ARR) of 0.60, 0.63 and 0.78 in patients taking 44 mcg, 22 mcg and placebo respectively, demonstrating the importance of early intervention. Additionally, patients taking the higher dosage of 44 mcg thrice weekly showed less progression versus those in the late treatment group. Data obtained following the 8-year extension trials also showed a reduction in disease progression with approximately 20% of patients deemed to have SPMS upon completion of the extended study.³,³⁴

Rebif® is supplied as a sterile, pre-filled syringe, or as a preassembled, ready to use autoinjector known as Rebif® Rebidose® (Table 1). Titration packs are available and recommended for both dosage regimens.³² Side effects are similar to those of other interferons (Table 2).³,⁸,³² However, ISRs are the most prevalent and may be the reason for many to discontinue use. Warnings included on the prescribing information include those for depression, suicide, hepatic injury, anaphylaxis and CJD due to human albumin content in Rebif®.¹,³,³² Due to the side effect profile, liver function tests should be taken 1, 3, and 6 months following initiation of the drug and rechecked periodically. Monitoring CBC with differential and platelet counts are warranted in those patients with myelosuppression. Moreover,
patients with a history of thyroid dysfunction should have thyroid function tests every 6 months or as needed. MS Lifelines® is available to patients who are in need of financial assistance, injection training, and/or nurse support and may be reached at 1-877-447-3243.

**Copaxone® (Glatiramer acetate)**

Approved for use in 1996 for RRMS, Copaxone® is a synthetically produced chain of amino acids that closely resembles human myelin basic protein (MBP). Containing L-glutamic acid, L-alanine, L-tyrosine, and L-lysine in random polymerized sequence, Copaxone® has been approved to reduce the frequency of relapses along with use in patients who have experienced a first clinical episode with MRI findings indicative of MS. Theories suggest immunomodulatory effects like high binding capacity for the Major Histocompatibility Complex class II molecules as a possible mechanism of action. Working in the periphery, Copaxone® is thought to increase suppressor T-cells, and enhance anti-inflammatory cytokines (IL-4, IL-5, IL-10, transforming growth factor-β). The anti-inflammatory responses seen are thought to cross the BBB, decreasing CNS inflammation. Antibodies against Copaxone® tend to develop 3 to 6 months after initiation; yet, efficacy is not thought to be affected. Brain-derived neurotrophic factor (BDNF), critical for neuronal and glial cell survival, are reportedly increased with Copaxone® use, and decreased amounts of black hole formation, known to correlate with irreversible disability, have been reported. Additionally, relapse rates, reduced by up to 32%, are comparable to other DMTs. However, one long-term clinical study reported 79.2%, 81.6%, 62% and 57% reductions in EDSS at 24 months, 35 months, 10 years and 15 years respectively, and approximately 35% of patients progressed to SPMS in the 15 year time frame.

Copaxone® was originally approved as a 20 mg daily subcutaneous injection. In January of 2014, Teva Pharmaceutical Industries announced the approval of a 40 mg/mL dose given subcutaneously three times weekly and reducing the number of overall injections. Storage and special requirements for
both dosage strengths are listed in Table 1.\textsuperscript{35} Side effects are frequent, ranging mostly from mild to moderate in severity, with ISRs being experienced in up to 71\% of patients (Table 2).\textsuperscript{35,36,39,43} Warnings and precautions to use include immediate post-injection reactions, chest pain, lipoatrophy and skin necrosis along with an unknown potential for effects on the immune response. Immediate post-injection reactions, occurring in up to 38\% of patients, consists of facial flushing, chest tightness, anxiety, and heart palpitations emerging seconds to 30 minutes post injection. While most resolve without clinical intervention, the newly released 40 mg dose has reported the need for emergency assistance during postmarket surveillance.\textsuperscript{35,36,41} Lipoatrophy, although uncommon, is deemed permanent with no known therapy. Proper injection technique and rotation of injection sites are thought to reduce both lipoatrophy and the rare occurrence of skin necrosis.\textsuperscript{35,39,43} As a benefit to patients, Teva Pharmaceutical Industries has created the Shared Solutions\textsuperscript{®} program. Patients, caregivers, friends and family members may call for support, injection training, immediate access to nurses, delivery of medicine directly to the home as well as receiving assistance with financial or insurance issues that may arise. Patients may enroll in the Shared Solutions\textsuperscript{®} program at 1-800-887-8100.\textsuperscript{42}

\textbf{Gilenya\textsuperscript{®} (Fingolimod).}

Initially studied in the early 1990s, Gilenya\textsuperscript{®} was derived from the entomopathogenic fungus called Isaria sinclairii.\textsuperscript{44} Approved in September of 2010, Gilenya\textsuperscript{®} became the first FDA approved oral DMT for MS. Indicated for RRMS, Gilenya\textsuperscript{®} reduces the frequency of relapses and delays progression through sphingosine-1-phosphate receptor modulation. Gilenya\textsuperscript{®} is a prodrug rapidly metabolized through phosphorylation. Its active metabolite fingolimod-phosphate binds with high affinity to sphingosine-1-phosphate receptors resulting in their internalization, reducing lymphocyte departure from lymph nodes and decreasing autoreactive lymphocytes from reaching the CNS.\textsuperscript{4,44-47} Reports state peripheral lymphocyte count reductions are seen within hours of administration, reducing baseline
levels by 20% to 30% after several weeks.⁴⁴,⁴⁷ Affecting predominantly T cells, Gilenya® reduces the amount of T_h17 cells thought to play a role in MS pathology. An additional effect shows inhibition of B cell trafficking. However, T cell activation, proliferation and differentiation by B cells appear to be unaffected. Furthermore, up to 30% of T cells are immune to the effects of Gilenya®, allowing for partial protection against infections. Scientists believe that given this effect Gilenya® is not a potent immunosuppressant.⁴⁴

Clinical efficacy studies have reported positive results in relation to annualized relapse rates (ARR), disability progression, and MRI results. One clinical trial displayed an ARR reduction of 0.16 to 0.20 versus placebo (0.40) and interferon beta-1a (0.33) while keeping up to 83% of patients relapse free over a 24-month period.⁴⁴ Moreover, reductions in EDSS disability progression, and numbers of new or enlarged T2 lesions were observed in 50% of the patients while numbers of T1 gadolinium-enhanced lesion reductions (90%) and brain volume loss were also noted.⁴,⁴⁴,⁴⁸ Even with established efficacy, Gilenya® has not been approved as a first-line agent. Target populations are considered individuals not responding to other established DMTs until further long-term clinical trials are completed.⁴⁴

Safety and tolerability data list bradyarrhythmias, infections, macular edema, fetal risk, respiratory, hepatic, and blood pressure effects as possible serious issues (Table 2).⁴,⁴⁸ Contraindications to use include myocardial infarction, Class III/IV heart failure, and a history of AVB.⁴,⁴⁴-⁴⁷ Since side effects may be significant, laboratory monitoring is warranted. Liver function tests beginning 6 months prior to initiation of medication should include liver transaminase and bilirubin levels with additional testing if hepatic injury is suspected during treatment. Prescribing information recommends discontinuing if serious hepatic injury has occurred. Clinical trials delineated liver enzymes ≥5-times the upper limit of normal as the cut-off point. Additionally, a CBC prior to initiating therapy and monitoring
for signs and symptoms of infections during treatment and two months following discontinuation is strongly recommended. Patients who have an active or chronic infection should delay initiation of Gilenya®. Moreover, varicella zoster antibody testing should be done in patients without a history of chickenpox or vaccination, and a 1-month waiting period prior to starting Gilenya® is strongly recommended to allow for proper antibody production. Immunizations with certain vaccines (keyhole limpet hemocyanin and pneumococcal polysaccharide) show a reduced and delayed response while taking Gilenya®. Furthermore, avoidance of live-attenuated vaccines for up to 2 months post discontinuation are recommended. Other considerations and recommendations for initiation of Gilenya® include ophthalmologic evaluations prior to starting therapy and performed 3 to 4 months thereafter. Additional ophthalmic tests monitoring visual acuity should be performed during routine evaluations and when visual disturbances are reported. Diabetic patients and those with a history of uveitis are at an increased risk for macular edema and should have regular ophthalmic evaluations. Pulmonary function tests need to be performed when clinically indicated and women of childbearing age should use contraception until 2 months post discontinuation. Additionally, blood pressure monitoring is warranted as mild increases have been reported.

Gilenya® is dispensed as a 28 or 7 capsule blister pack, and should be kept at room temperature (59°F-86°F), keeping away from moisture. Gilenya®, taken once daily, may be administered with or without food. The first dose should be done in a clinical setting equipped to manage bradycardia symptoms, using hourly blood pressure and pulse measurements. An echocardiogram is recommended prior to taking the first dose and at the end of the 6 hour observation period. Additional monitoring is warranted if heart rate is < 45 bpm 6 hours post dose, maximum decrease has not yet been reached 6 hours post dose, or ECG changes are noted 6 hours post dosage. Important drug-drug interactions exist for Gilenya® and include, yet are not limited to, ketoconazole, vaccinations, beta blockers, and other immunosuppressive medications.
Aubagio® (teriflunomide)

Aubagio® is another oral DMT for the treatment of RRMS. Exhibiting immunomodulatory and anti-inflammatory effects, Aubagio® is an active metabolite of leflunomide. It is classified as being an inhibitor of dihydro-orotate dehydrogenase (DHODH) through reversibly and noncompetitively binding to a ubiquinone binding site, and thus preventing pyrimidine synthesis involved in DNA synthesis.\(^5,49,50\)

Consequently, it decreases activation, proliferation and function of rapidly producing T and B lymphocytes in the periphery while leaving slowly dividing cells unaffected. While the exact MOA is unknown, theories suggest it produces an anti-inflammatory response by decreasing autoreactive T cells and cytokines crossing the BBB responsible for neuronal damage and progression of MS. It also increases anti-inflammatory cytokines in a dose-dependent manner.\(^49-51\) Additionally, Aubagio® is thought to prevent autoreactive T cells from interacting with antigen presenting cells. Animal studies have reported inhibition of tyrosine kinase, facor-κB, cyclooxygenase-2 among other proteins at a much lower binding affinity than for DHODH, but at therapeutic concentrations DHODH actions would predominate.\(^49\) Clinical efficacy data report relative risk reduction rates between 22% and 36% for both the 7 and 14 mg tablets. MRI reported T1 gadolinium-enhanced and T2 lesions were reduced by as much as 84%, and an ARR ranging from 0.279 and 0.370 for the 7 mg dose and 0.200 and 0.369 for the 14 mg dose. Although, the relative risk reduction was the same for both dosages at 31%.\(^5,49,50\)

Aubagio® is manufactured as 7mg and 14mg tablets given once daily with or without food. Having a long half-life (\(>14\) days), steady-state concentrations may be achieved in approximately 3 months. Aubagio® is highly protein bound (\(>99\%\)) and metabolized primarily through hydrolysis with biotransformation by oxidation considered a minor pathway. Primary elimination of unchanged drug occurs through biliary excretion while metabolites are renally excreted. Accelerated elimination is
achieved using cholestyramine or activated charcoal which reduces hepatobiliary recycling.\textsuperscript{5,49,50} Contraindications include severe hepatic disease, pregnancy and current leflunomide use.\textsuperscript{5}

Aubagio\textsuperscript{®} has a list of precautions, warnings, and side effects (Table 2).\textsuperscript{5,48-50} Due to the teratogenicity of the medication, women of childbearing age should use reliable contraception, and accelerated elimination in those wanting to conceive. The long half-life keeps unsafe concentrations in the body for up to 2 years after discontinuation without a washout period.\textsuperscript{5,49} Laboratory monitoring of transaminase, bilirubin levels and CBC within 6 months prior to initiation of Aubagio\textsuperscript{®} are recommended, and patients should be encouraged to report the first signs of infection to their physician as serious and fatal infections have been observed in postmarketing surveillance. Transaminase and bilirubin levels should be continued monthly for at least the first 6 months of administration while CBC is recommended upon signs/symptoms of infection. Tuberculosis skin tests should be completed prior to treatment due to increased incidences while taking Aubagio\textsuperscript{®}. Furthermore, blood pressure checks are recommended prior to therapy and periodically during treatment due to the observance of reported elevations during clinical trials.\textsuperscript{5,48,50}

Known drug-drug interactions have been reported even though it is not metabolized by any of the cytochrome P450 enzymes. Substrates of CYP2C8 (repaglinide, paclitaxel, pioglitazone, rosiglitazone) may experience an increase in levels due to Aubagio\textsuperscript{®} inhibition. CYP1A2 substrates (duloxetine, alosetron, theophylline, tizanidine) may experience decreased efficacy and levels. Warfarin international normalized ratios (INRs) show approximately a 25% decrease due to CYP2C9 induction. Moreover, patients are at increased risk of bleeding if Aubagio\textsuperscript{®} doses are missed. Ethinylestradiol and levonorgestrel serum concentrations are reportedly elevated leading to adverse effects, increasing the importance of proper oral contraception selection. Elevated concentrations of Aubagio\textsuperscript{®} are seen in response to efflux transporter breast cancer-resistant protein (BCRP) inhibitors such as cyclosporine and
gefitinib. Additionally, prescribing information recommends avoiding live vaccinations while taking Aubagio®.

**Tecfidera® (dimethyl fumarate).**

One of the latest approvals for MS, Tecfidera® was authorized by the FDA for use in RRMS. While the exact MOA is unknown, theories suggest it mediates oxidative stress, cellular injury and suppresses proinflammatory factors, slowing down the demyelination process and axonal loss. Nitric oxide, while having beneficial antimicrobial effects, reacts as a cytotoxic agent in MS, leading to extensive inflammation and axonal degeneration. Reportedly, Tecfidera® and the active metabolite, monomethyl fumarate (MMF), both activate the nuclear factor-erythroid 2–related factor (Nrf2). Considered to be a transcription factor having antioxidant actions, it reduces free radicals and reactive nitrogen species, protects the BBB, and helps to prevent myelin degradation. Tecfidera® is also thought to inhibit inflammatory cytokines and adhesion molecules responsible for MS progression. Two major studies recorded efficacious reductions in ARR of dimethyl fumarate versus placebo or glatiramer acetate in up to 53% of patients. Confirmed disability progression was reduced by 38%, and reductions of up to 85% in T2-weighted MRI lesions were reported. The T1-weighted MRI results decreased by 57%, and a 90% reduction in the odds of having an increase in gadolinium-enhanced T1 lesions was also recorded.

Another oral option, Tecfidera® comes in delayed-release capsules with a starting dose of 120 mg twice daily for 7 days followed by the maintenance dose of 240 mg twice daily taken with or without food. Capsules should be swallowed whole as chewing, crushing or sprinkling over food is not approved. Upon consumption, Tecfidera® is rapidly hydrolyzed by esterases found in the gastrointestinal tract, blood and tissues to its active metabolite MMF. Metabolism of MMF is done through the tricarboxylic acid cycle without cytochrome P450 involvement. In addition to MMF, fumaric acid, citric acid and
glucose are considered major metabolites. The primary route of elimination is through CO₂ exhalation accounting for up to 60% of the dose taken with minor elimination pathways being renal and fecal. Currently, there are no known drug interactions.⁶

The warnings and precautions section of the prescribing information is much shorter than other oral DMTs. Lymphopenia and flushing are considered the main adverse events (Table 2).⁶,⁵³-⁵⁵

According to prescribing information, the incidence of flushing, noted in approximately 40% of patients, may be reduced if taken with food.⁶,⁵² Flushing may begin within 30 minutes of administration and typically subsides within 90 minutes. Furthermore, the incidence of flushing tends to decrease with continued use.⁶,⁵³,⁵⁵ Tecfidera® has been shown to decrease lymphocytes and white blood cell counts especially during the first year of use and typically plateaus.⁶,⁵³,⁵⁴ Since lymphopenia may occur, a CBC count is necessary within 6 months prior to initiating treatment in addition to yearly monitoring or when indicated, and treatments withheld in the event of serious infections. While no opportunistic infections were noted during clinical trials, postmarketing surveillance has recorded cases of progressive multifocal leukoencephalopathy (PML) in psoriasis patients using compounded dimethyl fumarate, or dimethyl fumarate with other immunosuppressive medications.⁶,⁵¹,⁵²,⁵⁶ Caused by the reactivation of the JC polyomavirus (JCV) in immunocompromised patients, PML is a demyelinating infection responsible for destroying oligodendrocytes.⁵⁷,⁵⁸ Potentially fatal, patients that developed PML in the above case reports had been severely lymphopenic for extended periods of time which is known to increase the risk for PML. The recommended laboratory monitoring at baseline, yearly or when indicated would theoretically catch most cases of lymphopenia prior to reaching severe levels according to clinical scientists. Other studies researching animal toxicology and pharmacology data observed kidney toxicity with incidences of renal tubule epithelial injury. Additionally, cortical atrophy, interstitial fibrosis, and a dose-related increase in number and severity of retinal degeneration were noted at doses that were less
than or similar to human dosages. According to prescribing information, no studies have been performed in patients with renal or hepatic disease. 6,51,52,56

**Tysabri® (natalizumab)**

Tysabri®, produced in murine myeloma cells, is a humanized recombinant IgG4κ monoclonal antibody that binds to the α4-subunit of α4β1 and α4β7 integrins. These integrins, found on all leukocyte surfaces excluding neutrophils, assist autoreactive T cell migration into the CNS. Tysabri® binding of the α4-subunits inhibits interaction with cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (MAdCAM-1), decreasing the migration of autoreactive T cells from entering the CNS from peripheral circulation.57-59 Approved by the FDA in 2004, Tysabri® was quickly taken off the market approximately 3 months later due to concerns over the occurrence of PML in 3 patients. However, Tysabri® was allowed back onto the market after labeling changes to include a black boxed warning for PML and the creation of a strict distribution program called TOUCH® Prescribing Program. Under the program, registration of prescribers, infusion centers and pharmacies associated with the infusion centers is necessary for the ability to prescribe, distribute and infuse Tysabri®. Prescribers and patients must enroll into the program to completely understand the risks of treatment. Education of patients and prescribers, reporting of serious opportunistic infections like PML, and explicit guidelines to patient evaluations are all a part of the process of keeping patients safe.57,61

Tysabri® is approved for use as monotherapy in RRMS to reduce the frequency of relapses and disease progression. However, it is generally recognized as second-line therapy after inadequate responses from other DMTs, or in patients unable to tolerate other therapies. Efficacy data reveal significant reductions in ARR by as much as 68%, new or enlarged T₂-weighted hyperintense lesions by 83%, and gadolinium-enhanced T₁ lesions by up to 92%.57,58 However, one clinical trial reported treatment naïve patients with high disease activity displayed a reduction in ARR of 81%, and a 75%
decrease in the probability for relapse during a 2 year period, suggesting Tysabri® ought to be used first-line in patients with more aggressive disease during the first 12 to 24 months of therapy. Researchers go on to say that African Americans who traditionally present with more aggressive forms of RRMS have been shown in trials to have a reduced response to interferon therapy. Additionally, a 60% reduction in ARR, 79% reduction in mean gadolinium-enhanced T₁ lesions along with a 90% reduction in mean new or enlarged T₂-weighted hyperintense lesions have been reported in African Americans taking Tysabri®. Study clinicians suggest first-line therapy with Tysabri® should be considered in these patient populations with JCV antibody testing and frequent MRI screens every 3 to 4 months while taking Tysabri®. While some researchers promote first-line use of Tysabri®, others question its safety. Some researchers note interlaboratory variability exists detecting the JC virus, and MRI changes may be too subtle for even experienced neuroradiologists to detect PML, leaving patients at increased risk for fatal outcomes. Furthermore, a rebound effect has been reported in a small number of individuals that had only taken a few doses of Tysabri®, producing a significant increase in T₂-weighted hyperintense lesions upon discontinuation. Further research is recommended as this has only affected a small number of individuals, but would most likely be seen approximately 2 to 6 months after discontinuation.

Given as a 300 mg intravenous infusion, Tysabri® must be infused over an hour period and never by bolus or IV push. Administration should always be performed within 8 hours of preparation, and patients should be monitored for an hour after infusion. Contraindications to use include hypersensitivity reaction or patients previously or currently having PML. Warnings and precautions include immunosuppression, infections and hepatotoxicity while less common side effects include malignancy (breast cancer) and herpes infections of the CNS (Table 2). Tysabri® is listed as pregnancy category C, and known drug interactions include concomitant immunosuppressants as the risk for PML is increased.
Novantrone® (mitoxantrone)

Initially approved as an antineoplastic medication for certain types of cancer, the indication for use in SPMS, PRMS, or worsening RRMS was granted in October 2000. However, Novantrone® has not been approved for use in PPMS. As an anthracenedione derivative, Novantrone® inhibits DNA-topoisomerase II and is an effective immunomodulator. In MS, the beneficial effects of improved neurological deficits and delays in the progression of the disease are believed to stem from the immunosuppressant properties of the drug. In antineoplastic studies, Novantrone® has been shown to promote macrophage-moderated suppression of autoreactive B cells and T cells. Although, the exact MOA in MS in unknown.

The MIMS trial (Mitoxantrone in secondary progressive multiple sclerosis) best describes Novantrone® efficacy in MS. Neurological disability progression and EDSS deterioration rates >1 were reported in only 8% of mitoxantrone users vs. 25% of those on placebo while 57% of mitoxantrone users were relapse free versus 36% on placebo. Fewer hospitalizations were reported in the mitoxantrone group (40%) versus placebo (67%), and MRI data showed a decrease in the incidence of new gadolinium-enhanced lesions (0% vs. 16% placebo).

The RENEW trial (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) evaluated Novantrone® over a 5-year period primarily looking at treatment side effects. Over 70% of participants received concomitant therapy with other DMTs such as Copaxone®(25.3%), methylprednisolone IV (21%), Avonex® (20.6%), Betaseron® (14.9%), Rebif® (11.8%), and oral prednisone (5.7%). Completion rates reached 34% with over half of the discontinuations related to physician decision and patient request. Of particular interest, LVEF (left ventricular ejection fraction) of <50% was reported in 5.3% and 5.6% of patients during treatment and the follow-up phase respectively. Approximately 2% of patients reported signs/symptoms of congestive heart failure (CHF) with
cumulative dose being the primary risk factor for experiencing cardiotoxicity. Other data suggest cardiotoxicity is most likely associated with previous cardiovascular disease, higher cumulative Novantrone® dosage, or prior use of anthracyclines. In addition to the reported cardiotoxicity, three patients in the RENEW trial reported therapy-related leukemia while an increased incidence of amenorrhea in women with regular (22%) or irregular (51%) menstruation was also reported.

The side effect profile is significant for a few warnings and a contraindication of hypersensitivity reaction (Table 2). In addition to the cardiotoxicity and secondary leukemia listed previously, a warning for extravasation during IV infusion is also included. In MS, Novantrone is infused as a 12mg/m² dose given over 5 to 15 minutes every 3 months. Only given through IV infusion, prescribing information emphasizes the importance of experienced physicians overseeing each administration. Due to the incidence of cardiotoxicity, all patients should have their LVEF evaluated prior to initiating therapy. If LVEF is considered under the normal limit, Novantrone® use should be avoided. Prescribing information recommends an ECG, reevaluation of LVEF and a physical examination along with a history of signs/symptoms of cardiac issues prior to each given dose. Discontinuation of Novantrone® is recommended in patients with either a significant drop in LVEF or a decrease below the lower limit of normal. If discontinued, assessment of LVEF on a yearly basis is necessary to monitor for late incidences of cardiotoxicity. Laboratory monitoring is necessary with CBC, platelets, and liver function tests strongly recommended prior to each dose. Furthermore, women of childbearing age, regardless of birth control measures, should have a pregnancy test prior to each dose. In patients with hepatic impairment, Novantrone® use should be avoided. Due to the inherent risks of Novantrone®, the lifetime dose in MS should not exceed 140 mg/m².

Medications for Symptom Control
Disease-modifying therapies are designed to slow the progression of disease as shown on relapse rates and MRI-associated activity. Since they are not completely effective in their aim, axonal injury continues. Significantly impacting quality of life and being an essential part of patient care, there are many medications that are used in MS to combat symptomatic burden caused by the axonal injury. Affected areas of the body include bladder/bowel dysfunction, sexual and cognitive dysfunction, pain, mood disorders, fatigue, spasticity, tremor, and impaired gait. Many patients will experience several of these issues as early one year after diagnosis.\textsuperscript{7,70}

**Neurogenic bladder**

Affecting more than 70% of patients, neurogenic bladder is categorized as either a failure to store or a failure to empty. Symptoms alone cannot determine type.\textsuperscript{7} Detrusor-sphincter dyssnergia (DSD) is one of the main bladder disorders experienced in MS. DSD results due to suprasacral lesions that cause a failure to empty, leading to symptoms of urgency, frequency, incontinence, and urinary retention. Over 50% of untreated patients will develop severe complications like renal scarring and failure.\textsuperscript{71} Other types of bladder dysfunction in MS include detrusor hyperreflexia due to suprasacral cord lesions or suprapontine cerebral lesions, and a hypotonic, overly compliant bladder due to sacral cord lesions with both types resulting in a failure-to-store.\textsuperscript{7}

A urinalysis and culture must be done to rule out urinary tract infections, and treatment with antibiotics has been effective in some patients. Other patients will need an ultrasound to obtain the post-void residual urine volume (PVR). If \(<100\ \text{mL}\) is present, patients have a failure to store, and those with a volume \(>100\ \text{mL}\) would signify a failure to empty. Treatment in those patients with a failure to store consists of anticholinergic medications, intranasal desmopressin, and botulinum toxin A (Table 3).\textsuperscript{7,71} Clean intermittent straight catheterization is recommended in patients with a failure to empty.
Tamsulosin has also been used to some success. Patients with DSD that leads to both a failure to empty and urinary retention may benefit from a combination of catheterization and anticholinergic agents.  

**Neurogenic bowel**

Between 39% to 73% of patients will experience constipation, fecal incontinence or a combination of both in MS. Management of constipation consists of non-pharmacological options that include timed bathroom visits, physical exercises, dietary fiber, and adequate hydration. Pharmacological interventions include enemas, stool softeners, laxatives, and rectal stimulants (Table 3). Caution is warranted in patients treated for neurogenic bladder, spasticity and mood disorder as anticholinergics, antidepressants, and antispasticity medications can exacerbate constipation. Antidiarrheal and anticholinergic agents may be used for fecal incontinence.

**Spasticity**

Approximately 70% to 80% of patients will experience spasticity along the course of the disease. Increased muscle tone and resistance to passive movements leads to muscle spasms that plague patients with MS. As a result of upper motor neuron (UMN) lesions, spasticity ranges from mild to severe, leading to contractures if left untreated. Although considered an issue, patients may become dependent upon spasticity in order to stand or even walk, necessitating treatment options be guided according to the individual patient needs. Goals of treatment should incorporate the patient and focus on relief of discomfort, and improvements in daily living, walking, standing and sitting. Before initiating treatment, certain clinical conditions should be ruled out such as urinary tract infections, fractures, urolithiasis and constipation as they can trigger and exacerbate spasticity, and expectations of treatment should be discussed as complete remission is rare. Medicinal selection should be based upon disease severity, and duration along with consideration of severity and main areas of spasticity.
Medicinal agents used in treating spasticity include tizanidine, benzodiazepines, gabapentin/pregabalin, dantrolene, botulinum toxin, intrathecal baclofen with oral baclofen being considered first-line therapy in many patients (Table 3).\textsuperscript{7,71,72} Unfortunately, weakness and sedation are side effects to many of these medications with botulinum toxin being the exception.\textsuperscript{7,72} However, weakness experienced is theorized to be related to underlying UMN lesions and not necessarily as a direct effect from the medication. Moreover, sudden withdrawal of the medication may lead to rebound spasticity, necessitating a tapering of the dosage prior to switching medications. Additionally, combination therapy with two antispastic medications is recommended in the event of no response.\textsuperscript{72} Non-pharmacologic physiotherapy should be used concomitantly with medicinal treatments for optimum results. Stretching, exercise, physical and occupational therapy are essential in improving QoL and reducing the degree of spasticity experienced.\textsuperscript{7,71,72}

\textbf{Sexual dysfunction}

Sexual dysfunction is not only common in MS, but it is also rarely discussed. Between 40\% to 85\% of women and 50\% to 90\% of men with MS are affected. Several culprits of sexual dysfunction range from the disease itself, fatigue, depression, bladder problems, spasticity and even the medications to treat the disease and symptoms.\textsuperscript{7,72} Women report symptoms of decreased libido and vaginal secretions, abnormal sensation, and anorgasmia. No established medicinal treatments have been determined in women while men experiencing decreased libido, and erectile dysfunction may use Viagra\textsuperscript{®} with variable success rates (Table 3). Non-pharmacologic treatments for men include intracavernous vasodilator agents and vacuum-based penile prosthetics. Vaginal lubricants and external vibratory stimulators are recommended in women.\textsuperscript{7}

\textbf{Cognitive dysfunction.}
Patients with MS suffer from memory lapses, difficulties in sustained attention, processing of information with impaired memory being the most commonly experienced issue (40%-65%).

Approximately 70% of patients will experience some form of cognitive dysfunction over the course of the disease with weak correlation between disease duration and physical disability. However, cognitive dysfunction can be worsened by fatigue and depression and may significantly impact the patient’s ability to drive, cook or perform other daily tasks. Neuropsychological testing is recommended to identify impairment in addition to self-reported assessments and those of family members or caregivers. Both assessments are recommended as pain and depression may mask the ability to completely determine the severity of cognitive dysfunction. Treatment of depression and fatigue are strongly recommended as they play a critical role in exacerbating cognitive dysfunction. However, medicinal treatment options are lacking in this particular venue of MS. Clinical trials have studied memantine, donepezil, amantadine, and ginkgo biloba without showing proven efficacy even though a very small study of donepezil initially showed improvement.

Pain.

A common problem in MS, pain is an acute and chronic condition in approximately 86% of patients. Pain is classified as being nociceptive, neuropathic, and/or psychogenic. Nociceptive pain is due to the physiological response to tissue damage while neuropathic refers to pain stemming from a lesion or disease, creating a persistent burning sensation. Psychogenic pain is due to an emotional response and not that of an injury. Those with MS may experience a combination of pain types with the origin of pain being critical for proper management. The most common neuropathic pain experienced in MS is typically divided into dysesthetic limb pain, trigeminal neuralgia (TN), and Lhermitte phenomenon. Particular classes of medications most commonly used include tricyclic antidepressants, antiepileptic medications and even benzodiazepines (Table 3).
Mood Disorders.

Psychiatric disorders in MS are elevated compared to the general public. Incidences of major depressive disorder, adjustment disorders, anxiety disorders and bipolar disorders are increased with suicide being twice the norm.\textsuperscript{7,76,77} While depression and anxiety are the most commonly seen in MS, pseudobulbar affect, irritability and agitation are also experienced. However, many of these disorders go undiagnosed and either untreated or under treated. Lack of treatment or under treatment of mood disorders decrease QoL, and reduce adherence, leading to decreased functioning. Detection is critical to overall patient health.\textsuperscript{7,76} While there are few studies on non-pharmacologic and pharmacologic treatments, recommendations for treatment include cognitive behavioral therapy in addition to antidepressant medications (Table 3).\textsuperscript{7,76,77}

Fatigue

Over 90% of patients experience fatigue at some point with up to 50% stating it is the most bothersome symptom. The exact mechanism in MS is undetermined. However, it seems to be more prevalent in the afternoons, amplified by heat and associated with depression. Non-pharmacologic treatments include such things as getting adequate sleep, keeping cool with fans, and daytime naps. Exercise, approved by a physician, may also help alleviate daytime fatigue. Medicinal treatment with amantadine has shown some success while modafinil, methylphenidate and dextroamphetamine have been used with varying degrees of efficacy (Table 3).\textsuperscript{7,77}

Tremor/Ataxia

Another prominent symptom seen in up to 80% of MS patients is tremor. Brought about by cerebellar efferent pathway dysfunction, the disorder appears to be rather resistant to medicinal treatment. Other interventions used to lessen tremor include joint stabilization procedures, limb
weights, surgery and deep brain stimulation. Surgical procedure adverse effects may result in hemiparesis, dysphasia, dysphagia and paresthesias.\textsuperscript{7,77}

Ataxia is similar to tremor except it relates to a group of abnormal movements such as delay in movement and incoordination in addition to tremor. Approximately 85\% of patients will experience ataxia with up to 32\% considered severe. Unfortunately, good data on efficacy and safety is lacking in MS, but neurosurgery and rehabilitation measures are thought to show partial benefits.\textsuperscript{77}

**Multiple Sclerosis Is a Complicated Disease with Many Symptoms**

Disease-modifying medications are the mainstay of treatment in someone diagnosed with MS. Beta interferons along with other immunosuppressant medications have helped improve QoL while slowing down progression of the disease and disease burden. However, with any medication, side effects abound with some being rather severe and even life-threatening. Neutralizing antibodies may limit the effectiveness of the interferon therapies while the risk of PML impacts the duration of use for others. Laboratory monitoring for most of the DMTs is warranted to avoid severe and life-threatening events and reactions. Although, the progression of MS is delayed while using these DMTs, it cannot erase flares or symptoms of disease altogether. Symptom control becomes just as important as disease control in the eyes of the patient. Research in MS continues in the hope of finding a medicine that can put this disease into complete remission.
<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>STORAGE REQUIREMENTS</th>
<th>NEEDLE REQUIREMENTS</th>
<th>SPECIAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex®</td>
<td>LYO&lt;sup&gt;a&lt;/sup&gt; – Refrigerate (36°F-46°F) OR room temperature (77°F) ≤30 days</td>
<td>LYO&lt;sup&gt;a&lt;/sup&gt;/PFS&lt;sup&gt;b&lt;/sup&gt; – 23 gauge, 1¼ inch</td>
<td>Single use needles</td>
</tr>
<tr>
<td></td>
<td>Reconstituted LYO – Refrigerate ≤6 hours</td>
<td>Pen – 25 gauge, ¾ inch</td>
<td>Dispose needles according to state standards</td>
</tr>
<tr>
<td></td>
<td>PFS&lt;sup&gt;b&lt;/sup&gt; – Refrigerate (36°F-46°F) OR room temperature up to 7 days</td>
<td></td>
<td>Do not expose Avonex® to extreme temperatures</td>
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<td></td>
<td></td>
<td></td>
<td>Allow Avonex® 30 minutes to warm up naturally to room temperature prior to injecting</td>
</tr>
<tr>
<td>Betaseron®/Extavia®</td>
<td>LYO&lt;sup&gt;a&lt;/sup&gt; – Stable if kept between 59°F-86°F for ≤3 months</td>
<td>LYO&lt;sup&gt;a&lt;/sup&gt; – 30 gauge subcutaneous</td>
<td>Rotate injection sites</td>
</tr>
<tr>
<td></td>
<td>Room temperature (68°F-77°F) preferred</td>
<td></td>
<td>6-week titration schedule</td>
</tr>
<tr>
<td></td>
<td>Reconstituted LYO&lt;sup&gt;a&lt;/sup&gt; – Refrigerate ≤3 hours</td>
<td></td>
<td>Keep 48 hours between dosing</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dispose needles according to state standards</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rotate injection sites</td>
</tr>
<tr>
<td>Rebif®</td>
<td>PFS&lt;sup&gt;b&lt;/sup&gt;/Rebidose – Refrigerate (36°F-46°F) OR room temperature (77°F) ≤30 days</td>
<td>PFS&lt;sup&gt;b&lt;/sup&gt;/Rebidose autoinjector – 29 gauge, ½ inch</td>
<td>Preservative free, single use</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Keep 48 hours between dosing</td>
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<td></td>
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<td></td>
<td>Dispose needles according to state standards</td>
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<td></td>
<td></td>
<td>Do not expose to extreme temperatures or light</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Allow 30 minutes to warm up naturally to room temperature prior to injecting</td>
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</table>
### Copaxone®

<table>
<thead>
<tr>
<th>PFS&lt;sup&gt;b&lt;/sup&gt; – Refrigerate (36°F-46°F) OR 59°F-86°F up to a month</th>
<th>PFS&lt;sup&gt;b&lt;/sup&gt; – subcutaneous needle</th>
<th>Rotate injection sites</th>
<th>20 mg dose is daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg dose is three times weekly on scheduled days</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dispose needles according to state standards</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not expose to extreme temperatures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allow 30 minutes to warm up naturally to room temperature prior to injecting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotate injection sites</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Source: References: 22-24, 25, 29, 30, 32, 35*

<sup>a</sup>LYO=Lyophilized

<sup>b</sup>PFS=Prefilled Syringe

### Table 2. DMARDs Side Effect Profiles

<table>
<thead>
<tr>
<th>DMARD</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex®&lt;sup&gt;a&lt;/sup&gt;</td>
<td>FLS&lt;sup&gt;a&lt;/sup&gt;, Headache, Myalgia/muscle aches, Arthralgia, Depression, Suicidal ideation, ISRs&lt;sup&gt;b&lt;/sup&gt;, Fatigue, Fever, Nausea, Diarrhea, Chills, Nasopharyngitis, Hepatic failure, Hepatitis, ↑ hepatic enzyme levels, Seizures, CHF, Cardiomyopathy, Anaphylaxis</td>
</tr>
<tr>
<td>Betaseron®/Extavia®&lt;sup&gt;a&lt;/sup&gt;</td>
<td>FLS&lt;sup&gt;a&lt;/sup&gt;, ISRs, Asthenia, Headache, Leukopenia, ↑LFTs&lt;sup&gt;d&lt;/sup&gt;, asthenia, hypertonia, myasthenia, fever, chills, myalgia, arthralgia, malaise/fatigue, lymphopenia, depression, suicidal ideation, injection-site necrosis, CHF, Cardiomyopathy, Anaphylaxis, Seizures</td>
</tr>
<tr>
<td>Rebif®</td>
<td>ISRs&lt;sup&gt;b&lt;/sup&gt;, FLS&lt;sup&gt;a&lt;/sup&gt;, Depression, Suicidal ideation, ↑LFTs&lt;sup&gt;d&lt;/sup&gt;, Leukopenia, Lymphopenia, Fever, Nausea, Myalgia, Headache, Fatigue, Sweating, Seizures, Anaphylaxis</td>
</tr>
<tr>
<td>Copaxone®&lt;sup&gt;a&lt;/sup&gt;</td>
<td>FLS&lt;sup&gt;a&lt;/sup&gt;, ISRs&lt;sup&gt;b&lt;/sup&gt;, Facial flushing, Chest tightness, Dyspnea, Palpitations, Tachycardia, Anxiety, Arthralgia, Back pain, Depression, Skin necrosis, Lipoatrophy, Fever, Chills, Upper respiratory tract infection, Anaphylaxis</td>
</tr>
</tbody>
</table>
### Table 3. SYMPTOM CONTROL MEDICATIONS

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gilenya® (fingolimod)</strong></td>
<td>Nasopharyngitis, Dyspnea, Headache, Diarrhea, Nausea, FLS(^a), Enterocolitis, Asymptomatic lymphopenia, ↑LFTs(^d), Lymphopenia, Back pain, Transient bradycardia, Cough, Lower respiratory infection, AV(^e) block, Hypertension, Macular edema, Skin cancer, Disseminated primary varicella zoster, Herpes simplex encephalitis</td>
</tr>
<tr>
<td><strong>Aubagio® (teriflunomide)</strong></td>
<td>↑LFTs(^d), Alopecia, Arthralgia, back/limb pain, Diarrhea, Constipation, Nausea, Fatigue, Urinary tract infection, Rash, Nasopharyngitis, Neutropenia, Paraesthesia, Rhabdomyolysis, Trigeminal neuralgia, Malignant neoplasms, Acute renal failure, Hyperkalemia, ↑BP(^f)</td>
</tr>
<tr>
<td><strong>Tecfidera® (dimethyl fumarate)</strong></td>
<td>Flushing, Diarrhea, Nausea, Vomiting, Abdominal pain, Upper respiratory tract infections, Erythema, Proteinuria, Pruritus, Lymphopenia, ↑LFTs(^d)</td>
</tr>
<tr>
<td><strong>Tysabri® (natalizumab)</strong></td>
<td>Headache, Fatigue, Depression, Arthralgia, UTI(^g), Respiratory tract infection, Herpes infections, Vaginitis, Gastroenteritis, Pain in extremity, abdominal pain, Diarrhea, Rash, PML(^h), Malignancies</td>
</tr>
<tr>
<td><strong>Novantrone® (mitoxantrone)</strong></td>
<td>Nausea, UTI, Upper respiratory tract infection, Stomatitis, Arrhythmia, Diarrhea, Menstrual disorders, Amenorrhea, Alopecia, Leukopenia, Depression, ↓LVEF(^i), Bone pain, Vomiting, Renal failure, Extravasation, Secondary leukemia</td>
</tr>
</tbody>
</table>

**Source:** References: 1,3-6,8,13,22,14,25,28,31,32,35,36,39,43,48-50,53-55,57-59,64,66,68,69

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\(^a\)FLS=Flu-like symptoms  
\(^b\)ISRs=Injection site reactions  
\(^c\)CHF=Congestive heart failure  
\(^d\)LFTs=Liver Function Tests  
\(^e\)AV=Atrioventricular  
\(^f\)BP=Blood Pressure  
\(^g\)UTI=Urinary Tract Infection  
\(^h\)PML= Progressive Multifocal Leukoencephalopathy  
\(^i\)LVEF=Left Ventricular Ejection Fraction
| Ditropan XL (oxybutynin) | Contraindicated: |
| Enablex (darifenacin) | Glaucoma(narrow angled), Mechanical bladder outlet obstruction |
| Flomax (tamsulosin) | Avoid: |
| Hytrin (terazosin) | Nonselective agents in patients with cognitive dysfunction |
| Minipress (prazosin) | |
| Oxytrol (oxybutynin) | |
| Pro-Banthine (propantheline) | |
| Sanctura (trosipum chloride) | |
| Tofranil (imipramine) | |
| Vesicare (solifenacin succinate) | |

**NEUROGENIC BOWEL**

| Constipation: |
| Colace (docusate) |
| Dulcolax (bisacodyl) |
| Enemeez (docusate laxative) |
| Fleet Enema (sodium phosphate) |
| Metamucil |
| Phillips Milk of Magnesia (magnesium hydroxide) |
| Glycerin |

| Incontinence: |
| Loperamide |
| Anticholinergic medications |

**SPASTICITY**

| Botox (botulinum toxin) |
| Dantrium (dantrolene) |
| Gablofen (baclofen intrathecal) |
| Klonopin (clonazepam) |
| Lioresal (baclofen) |
| Neurontin (gabapentin) |
| Valium (diazepam) |
| Zanaflex (tizanidine) |

**SEXUAL DYSFUNCTION**

| Common SE$^a$ in men: |
| Headache, flushing, dyspepsia, priapism, ↓BP$^b$ |
| Men with cardiovascular disease should avoid using due to potential for cardiac events |

| Common SE$^a$: |
| Sedation, muscle weakness except for botulinum toxin |

| Men: |
| Cialis (tadalafil) |
| Levitra (vardenafil) |
| Papaverine |
| MUSE (alprostadil) |
| Prostin VR (alprostadil) |
| Viagra (sildenafil) |

| Women: |
| Vaginal lubricants (K-Y, Astroglide, Replens, Lubrin) |
### Pain

Dysesthetic limb pain:
- Aventyl (nortriptyline)
- Cymbalta (duloxetine)
- Effexor / Effexor XR (venlafaxine)
- Elavil (amitriptyline)
- Lamictal (lamotrigine)
- Lyrica (pregabalin)
- Neurontin (gabapentin)
- Pamelor (nortriptyline)

Trigeminal neuralgia (TN):
- Lamictal (lamotrigine)
- Lioresal (baclofen)
- Neurontin (gabapentin)
- Oxtellar XR (oxcarbazepine)
- Tegretol/XR (carbamazepine)
- Trileptal (oxcarbazepine)

Lhermitte phenomenon:
- Neurontin (gabapentin)
- Tegretol/XR (carbamazepine)

### Mood Disorders

#### First-Line Medications
- SSRIs:
  - Celexa (citalopram)
  - Luvox (fluvoxamine)
  - Paxil (paroxetine)
  - Prozac (fluoxetine)
  - Sarafem (fluoxetine)
  - Zoloft (sertraline)

#### Second-Line Medicines
- Tricyclic antidepressants:
  - Amitriptyline
  - Norpramin (desipramine)
  - Pamelor (nortriptyline)

#### Other:
- Wellbutrin (bupropion)

### Fatigue

- Amantadine
- Provigil (modafinil)
- Methylphenidate

- Modafinil, methylphenidate and dextroamphetamine

### Notes

- PDE5 inhibitors are contraindicated with nitrates
- Carbamazepine and oxcarbazepine are considered first-line medicines in TN
- Cognitive-behavioral psychotherapy in combination with medicinal treatment is recommended.
- Tricyclics and duloxetine are preferred if patient has comorbid neuropathic pain

- Moos MOS (citalopram)
Dextroamphetamine used with varying degrees of efficacy

Source: References: 7,71,72,74-77

aSE=Side Effects

bBP=Blood Pressure

cPDE5=Phosphodiesterase Type 5 Inhibitor

dSSRIs=Selective Serotonin Reuptake Inhibitors
References:


ACTIVITY TEST

1. Which medication is a non-glycosylated interferon?
   A. Avonex
   B. Rebif
   C. Betaseron
   D. Copaxone

2. Flu-like symptoms are most prevalent with which DMT?
   A. Gilenya
   B. Betaseron
   C. Avonex
   D. Rebif

3. What DMT medications contain human albumin?
   A. PFS Avonex, Betaseron, Rebif, Copaxone
   B. LYO Avonex, Betaseron, Rebif
   C. LYO Avonex, Copaxone, Rebif
   D. PFS Avonex, Copaxone, Rebif

4. What medication needs testing for varicella zoster antibodies prior to starting?
   A. Aubagio
   B. Tecfidera
   C. Gilenya
   D. Novantrone

5. Lyophilized Betaseron is best stored:
   A. Room temperature (68°F-77°F) up to 3 months
   B. 59°F-86°F up to 1 month
   C. Room temperature (68°F-77°F) up to 1 month
   D. Refrigerate (36°F-46°F) up to 7 days
6. Flushing and lymphopenia are considered the main side effects for which DMT:
   A. Gilenya
   B. Betaseron
   C. Tecfidera
   D. Tysabri

7. PML has been reported for the following medications:
   A. Novantrone, Tysabri
   B. Tysabri, Tecfidera
   C. Tecfidera, Gilenya
   D. Tysabri, Aubagio

8. Accelerated elimination with cholestyramine or activated charcoal is recommended for which DMT?
   A. Aubagio
   B. Tecfidera
   C. Gilenya
   D. Tysabri

9. What is the maximum lifetime dose in MS for Novantrone?
   A. 110 mg/m$^2$
   B. 120 mg/m$^2$
   C. 130 mg/m$^2$
   D. 140 mg/m$^2$

10. Researchers suggest African Americans with more aggressive forms of MS may respond more favorably to:
    A. Novantrone
    B. Avonex
    C. Tysabri
    D. Aubagio
11. All the following are true about Neurogenic bladder except:
   A. Detrusor-sphincter dyssnergia (DSD) is one of the most commonly experienced bladder disorders in MS
   B. Symptoms alone may determine type of bladder disorder
   C. Untreated DSD may lead to renal scarring and failure
   D. Other bladder disorders in MS include detrusor hyperreflexia and hypotonic, overly compliant

12. Which class of drugs exacerbate Neurogenic bowel?
   A. Antispastics
   B. Antiarrhythmics
   C. Calcium channel blockers
   D. Statins

13. Common side effects of antispastic medicines include:
   A. Insomnia, weakness
   B. Sedation, weakness
   C. Insomnia, agitation
   D. Sedation, agitation

14. The percentage of patients affected by cognitive dysfunction in MS is up to:
   A. 50%
   B. 60%
   C. 70%
   D. 80%

15. What medications are considered first-line treatment for Trigeminal Neuralgia pain:
   A. Carbamazepine, oxcarbazepine
   B. Cymbalta, Effexor
   C. Lyrica, Neurontin
   D. Aventyl, Elavil
16. What MS-associated condition is amplified by heat?
   A. Pain
   B. Tremor
   C. Spasticity
   D. Fatigue

17. Fatigue in MS may be alleviated by:
   A. Cymbalta
   B. Amytriptyline
   C. Zoloft
   D. Amantadine

18. Lhermitte phenomenon is best treated with:
   A. Neurontin, Tegretol
   B. Lioresal, Neurontin
   C. Lamictal, Lioresal
   D. Lyrica, Neurontin

19. Which of the interferon therapies has the lowest incidences of ISRs?
   A. Rebif
   B. Copaxone
   C. Avonex
   D. Betaseron

20. What DMT is a synthetically produced chain of amino acids?
   A. Aubagio
   B. Avonex
   C. Betaseron
   D. Copaxone

Please submit your final responses on freeCE.com. Thank you.