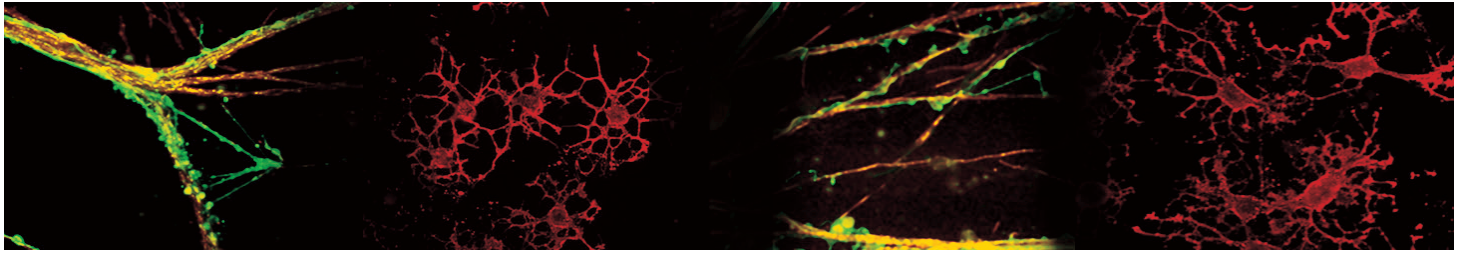

Multiple Sclerosis (MS)
Disease Modifying Therapy
A Reference Guide for Health Care Professionals

Cheryl Allin[1] BSP., Adil J. Nazarali[1*] Ph.D. MRPharmS., Jan Britz[2], R.N., MSCN., Walter J. Hader[2], MD, FRCPC
College of Pharmacy and Nutrition[1], University of Saskatchewan, Saskatoon, SK S7N 5C9 and Multiple Sclerosis Clinic, Saskatoon City Hospital[2], Saskatoon, SK S7K 0M7 Canada

MS: A disease of the brain and spinal cord, where the myelin that covers nerve cells becomes inflamed and is then destroyed forming plaques or scars (sclerosis).[1] Nerve cells are unable to communicate effectively when the myelin is destroyed, and this causes the symptoms of MS.[1] For example, if the myelin on vision axons is destroyed, vision will be affected. Some myelin destruction will be repaired by the body and improvement in the symptoms will occur, but in time losses in function accumulate.[1]

Disease Modifying Therapies: Currently five disease modifying medications are approved for use in Canada.[2] These medications are effective in reducing relapses, reducing new lesion formation as seen on an MRI, and slowing disability.[2] It is important to remember that these medications may delay the progression of the disease and patients most likely will not see improvement in symptoms they already have.[2]

Notes:

- **A comprehensive list of phrases, terms and abbreviations used throughout the reference guide is provided at the end along with further explanations to aid in understanding.**
- **Key points within sections are highlighted.**
- **This reference guide is set up in charts to ease comparison of the different disease modifying therapies.**
- **The tabs can be used to quickly guide the user to a specific section of interest.**

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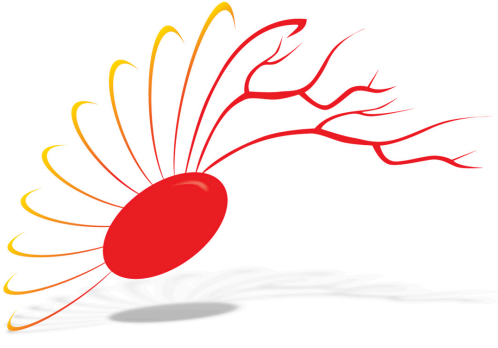

*** Inquiries can be made to Adil J. Nazarali at aj.nazarali@usask.ca or to Jan Britz at jan.britz@saskatoonhealthregion.ca**

	Betaseron® Interferon Beta 1b	**Rebif®** Interferon Beta 1a	**Avonex®** Interferon Beta 1a	**Copaxone®** Glatiramer Acetate	**Tysabri®** Natalizumab
Description	Interferon is produced by fibroblasts. It has been found to have not only antiviral and antiproliferative effects but also immunomodulatory effects. Produced in a bacterial expression system and is therefore not glycosylated.[3] Differs from naturally occurring human protein by a single amino acid substitution and the lack of carbohydrate side chains.[4]	Interferon is produced by fibroblasts. It has been found to have not only antiviral and antiproliferative effects but also immunomodulatory effects.[3] Produced in eukaryotic cell lines hence it is glycosylated, this may decrease aggregation and immunogenicity which may explain its higher biological potency in its antiviral activity than interferon beta 1b.[3] Represents the naturally occurring amino acid sequence.[3]		A mixture of polymers of four amino acids; L-alanine, L-glutamic acid, L-lysine and L-tyrosine; the resulting mixture is antigenically similar to myelin basic protein (MBP).[4] MBP is an important part of the myelin sheath.[4]	Recombinant humanized monoclonal antibody to the alpha-4 subunit of integrin molecules.[5] Integrins are important for adhesion and migration of cells from the vasculature into inflamed tissue.[4,5]
Mechanism of Action	**Immune Modulator:** *Blocks the activity of specific immune system cells and reduces the passage of these immune cells into the CNS (where they can cause inflammation and damage the myelin sheath).*[2] Immunomodulatory effects are believed to have the most impact on MS; this includes enhancing suppressor T cell activity, reducing proinflammatory cytokines, down-regulating antigen presentation, and reducing trafficking of lymphocytes into the CNS.[4]	**Immune Modulator:** *Blocks the activity of specific immune system cells and reduces the passage of these immune cells into the CNS (where they can cause inflammation and damage the myelin sheath).*[2] Alters the expression and response to surface antigens and can enhance immune cell activities.[4] Properties that modify biologic responses are mediated by cell surface receptor interactions.[4]	**Immune Modulator:** *Blocks the activity of specific immune system cells and reduces the passage of these immune cells into the CNS (where they can cause inflammation and damage the myelin sheath).*[2] Alters the expression and response to surface antigens and can enhance immune cell activities.[4] Properties that modify biologic responses are mediated by cell surface receptor interactions.[4]	**Immune Modulator:** *Induces the production of immune cells that are less damaging to the myelin sheath.*[2] Believed to induce and activate T-lymphocyte suppressor cells specific for a myelin antigen and interferes with the antigen-presenting function of certain immune cells opposing pathogenic T-cell function.[4]	**Selective Adhesion Molecule Inhibitor:** *Reduces the movement of active immune cells into the CNS, reducing inflammation and demyelination.*[6] Blocks integrin associated with vascular receptors, limiting adhesion and transmigration of leukocytes.[4] Efficacy may be related to blockade of T-lymphocyte migration into the CNS.[4]

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Effectiveness	→Interferon beta has been shown to reduce the attack rate (measured both clinically & by MRI) in patients with MS or with clinically isolated syndromes who are at high risk for developing MS.[7] Treatment of MS with interferon beta produces a beneficial effect on MRIs such as T2 disease burden and may also slow sustained disability progression.[7] Note: T2 lesions in relapsing-remitting MS correlate strongly with brain tissue loss and brain tissue integrity.[8] → Considering interferon beta for treatment is appropriate for any patient who is at high risk for developing CDMS, or who already has either RRMS or SPMS and is experiencing relapses.[7] The effectiveness of interferon Beta in patients with SPMS but without relapses is uncertain.[7] →It is possible that a dose-response curve is associated with the use of interferon beta for the treatment of MS. However, this dose-effect instead may be due to differences in the frequency of administration (rather than dose) between studies.[7] → The route of administration of interferon beta is probably not of clinical importance with regard to efficacy.[7] The side-effect profile differs between routes of administration. There is no known clinical difference between the different types of interferon beta, although this has not been thoroughly studied.[7]			→ Shown to reduce the attack rate (measured both clinically & by MRI) in patients with RRMS.[7] Treatment produces beneficial effects on MRI such as T2 disease burden, and may also slow sustained disability progression in RRMS.[7] → It is appropriate to consider for treatment in any patient who has RRMS.[7]	→Natalizumab reduced relapse rates by 67% and had beneficial effects on MRI measurements after one year in trial. Two year data shows it slows disability progression by 42%.[9]
Antibody Formation :	***Neutralizing Antibodies (NAb):*** Treatment of patients with MS with interferon beta is associated with the production of NAb.[7] NAbs production, however, is likely less with interferon beta 1a treatment than with interferon beta 1b treatment.[7] Avonex has been associated with the lowest incidence.[2] The biologic effect of NAb is uncertain although their presence may be associated with a reduction in clinical effectiveness of interferon beta treatment.[7] The finding of sustained high-titer NAb is associated with a reduction in the therapeutic effects of interferon beta on radiographic and clinical measures of MS disease activity.[10] The utilization of NAb testing is still controversial, and no specific recommendations on when to test, which test to use, how many tests are necessary, or the cut off titer are available.[10] Current Guidelines being implemented include the following criteria:[11] - To be considered for NAb testing, patient must be on interferon beta treatment continuously for at least 1 year, and in the physician's opinion must be doing poorly.[11] If a positive titer is obtained, the patient should be retested within 3 months.[11] Patients doing well need not be tested.[11] - After two consecutive titers at least three months apart, a NAb positive result can be determined.[11]			***Reactive Antibodies (IgG):*** Present in all treated patients.[12] Antibody profiles are similar in those who experience relapses and those who do not.[12] The ability of the antibodies to neutralize Copaxone is not exhibited,[12] and the significance of the antibodies is unknown.[2]	***Anti-natalizumab antibodies:*** Persistent antibodies were associated with decreased efficacy and increased incidence of hypersensitivity reactions.[5] Antibodies can be detected and confirmed with sequential serum antibody tests.[5] Antibodies detected early in treatment may be transient and disappear.[5] Recommended to retest 6 wks to 3 months after an initial positive test.[5] Consider stopping if antibodies remain persistent.[5]

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Warnings and Precautions	→Use with caution in patients with: -Hepatic impairment -Bone marrow suppression -Pre-existing cardiovascular disease -Respiratory disease -Renal impairment -History of seizure disorder[4] →Increased risk of infection.[4] →May experience increased spasticity.[13]	Use with caution in patients with: -Pre-existing cardiovascular disease, including angina, CHF, & arrhythmia. Rare cases of new-onset cardiomyopathy and CHF reported.[4] -Hepatic impairment or in those who abuse alcohol. Dose adjustment may be necessary.[4] -History of seizure disorder.[4] -Safety/efficacy not established in SPMS.[4] -May experience increased spasticity.[13]		-Immediate postinjection systemic reactions occur in 10% of patients; symptoms begin within minutes of injection and usually spontaneously resolve within 30 minutes.[4] Most patients only have one reaction despite repeated injections.[4]	-Antibody formation occurs in about 10% of patients and is associated with a decrease in Natalizumab levels and a decrease in efficacy.[4] -Increased risk of opportunistic infection.[4] -Safety and efficacy have not been established in SPMS for therapy longer than 2 years.[4] - There is an association with a small risk of developing PML.[9]
Interactions	Decreases the metabolism of theophylline derivatives.[4]	Increases the adverse/toxic effects of ACE inhibitors, specifically the development of granulocytopenia.[4] Hepatotoxic drugs may increase the risk of hepatic injury.[4] May increase the levels/effects of theophylline.[4] May increase the anticoagulant effects of warfarin.[4] May decrease the metabolism of zidovudine.[4] Need to monitor these potential interactions!		None Known	Therapy with immunosuppressants may increase the risk of infection.[4] Interferon beta-1a may increase the levels of Natalizumab.[4] Re: Only use as monotherapy
Psychiatric	Associated with severe psychiatric adverse events (psychosis, mania, depression, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms; avoid use in severe psychiatric disorders and use caution in patients with a history of depression; patients exhibiting symptoms of depression should be closely monitored and discontinuation of therapy considered.[4] Note: The incidence seems to be lower with Rebif® New Formulation.[14]			May cause anxiety or depression.[4]	May cause sedation.[4] Depression & suicidal ideation reported; use caution if history of depression.[4]
Pharmaco-kinetics/ Pharmaco-dynamics	*t½ elimination*: 8 min to 4.3 hrs *Time to peak serum*: 1-8hrs[4]	*t½ elimination*: 69 hrs *Time to peak serum*: 16 hrs[4]	*t½ elimination*: 10 hrs *Time to peak serum*: 3-15 hrs[4]	*Distribution*: Small amounts enter lymphatic circulation *Metabolism:* large % hydrolyzed locally[4]	*Distribution:* 3.8-7.6 L *t½ elimination*: 7-15 days *Excretion: Clearance:* 11-21mL/hr[4]

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Pregnancy and Lactation	Pregnancy Risk Factor C[4] A dose-related abortifacient activity was noted in Rhesus monkeys.[4] No adequate/well-controlled studies in pregnant women.[4] Treatment should be discontinued if a woman becomes pregnant, or plans to become pregnant.[4] Pregnant women can register at 1-800-478-7049 or at BetaseronPregnancyRegistry.com [15] **Excretion in breast milk** unknown/ contraindicated.[4] Its use has not been evaluated during lactation.[4]	Pregnancy Risk Factor C[4] No adequate/ well-controlled studies in pregnant women.[4] Consider stopping treatment if a woman becomes/plans pregnancy.[4] A dose-related abortifacient activity was noted in Rhesus monkeys.[4] Healthcare providers should register pregnant women receiving Rebif® at www.rebifpregnancyregistry.com or MS LifeLines1-877-44-REBIF[4] **Excretion in breast milk** unknown/not recommended Use has not been evaluated during lactation; either stop breast-feeding or discontinue the drug.[4]	Pregnancy Risk Factor C[4] No adequate/ well-controlled studies in pregnant women.[4] Consider stopping treatment if a woman becomes/plans to become pregnant.[4] A dose-related abortifacient activity was noted in Rhesus monkeys.[4] Enroll women who become pregnant while on Avonex® in the registry at 1-800-456-2255.[4] **Excretion in breast milk** unknown/not recommended Use has not been evaluated during lactation; either stop breast-feeding or discontinue the drug.[4]	Pregnancy risk factor B[4] Adverse events were not observed in animal studies.[4] No adequate/ well-controlled studies in pregnant women.[4] Use in pregnancy only if clearly necessary.[4] **Excretion in breast milk** unknown/use caution.[4]	Pregnancy Risk Factor C[4] Teratogenic effects not reported in animal studies; but a decrease in fetus survival was noted.[4] Crosses placenta in animals causing anemia and decreased platelet counts.[4] No adequate/well-controlled studies in pregnant women.[4] Use only if clearly needed. Enroll pregnant women in: Tysabri® Pregnancy Exposure Registry: 800-456-2255.[4] **Excretion in breast milk** unknown/not recommended Immunoglobulin may be excreted in breast milk.[4] Effects on infant are unknown. Consider stopping breast-feeding during treatment.[4]

FACT: A woman with RRMS will experience significantly less relapses during her pregnancy.[16] This reduction can be even more significant than the reduction seen with the available medications.[16] A spike in relapses may be seen after pregnancy for the first six months, and after this the regular disease pattern should continue.[16]

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Dose	-0.25mg (1ml) every other day[4] - Titrate up starting at ¼ the dose (0.25ml) for 1 week then ½ dose (0.5ml) for 1 week, then ¾ the dose (0.75ml) for 1 week, then full dose (1.0ml) at week 4.	-44 µg 3 times/wk or 22 µg 3 times/wk (separate doses by at least 48hrs) [4] -Titrate up starting at 8.8 µg 3 times/wk for 2 wks then 22 µg 3 times/wk for 2 wks[4] -If liver function tests increase or in case of leukopenia ↓ dose by 20-50% until resolved.[4]	30 µg once weekly [4]	20mg daily [4]	300mg once every 4 weeks[4]
Admin-istration	Subcutaneous injection[4] (under the skin)	Subcutaneous injection[4] (under the skin)	Intramuscular injection[4] (into the muscle)	Subcutaneous injection [4] (under the skin)	Intravenous infusion over 1 hour[4] (into the vein) at a specialized infusion centre.[2]
Preparation	Must be reconstituted prior to use[4] (autoinjector)	Prefilled syringes [4] (autoinjector)	Prefilled syringes [4] (personal injector)	Prefilled syringes [4] (autoinjector)	Must be reconstituted prior to use (dilute 300 mg in NS 100 mL, gently invert to mix).[4]
Storage	Room Temp (25 ºC) If not used immediately after reconstitution, must refrigerate (2-8ºC) and used within 3 hours. [6] Do not freeze or shake.[4]	Store in refrigerator (2-8ºC), or may be stored at or below 25ºC for up to 30 days away from heat and light. [6] Do not freeze, allow warming to room temperature prior to use. [4]	Store Prefilled syringes in refrigerator (2-8ºC) do not freeze. [4] Protect from light. Allow to warm to room temp prior to use. [4] Use within 12 hours after removing from fridge [4,37]	Store in refrigerator (2-8ºC) [4] or may be stored at or below 25ºC for up to 30 days away from heat and light. [4] Bring to room temp prior to use.[4]	Store concentrated solution under refrigeration (2-8ºC).[4] Do not freeze/shake, & protect from light. Following dilution, may store refrigerated for 8 hours. [4] Warm to room temp prior to use.[4]

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Indications **(refer to the MS Society's website for a breakdown of indications according to provinces)**	1) Treatment of relapsing forms of MS[17] 2) Treatment of first clinical episode with MRI features consistent with MS[17] 3) Treatment of Secondary Progressive MS with or without clinical attacks [17] Note: Not approved in all provinces. Check individual provincial formulary guidelines.	1) Treatment of relapsing forms of MS[17] 3) Treatment of Secondary Progressive MS with or without clinical attacks [17] Note: Not approved in all provinces. Check individual provincial formulary guidelines.	1) Treatment of relapsing forms of MS[17] 2) Treatment of first clinical episode with MRI features consistent with MS[17] 3) Treatment of Secondary Progressive MS with or without clinical attacks [17] Note: Not approved in all provinces. Check individual provincial formulary guidelines.	1) Management of relapsing remitting type MS[17] 2) Treatment of first clinical episode with MRI features consistent with MS[17] 3) Treatment of Secondary Progressive MS with or without clinical attacks [17] Note: Not approved in all provinces. Check individual provincial formulary guidelines.	1) Treatment of relapsing forms of MS[18] (For monotherapy treatment in patients with a diagnosis of MS who also meet **ALL** of the following criteria: a) Failure to respond to full and adequate courses of treatment with at least two disease-modifying therapies or have contraindications to, or be intolerant of these therapies, **AND** b) Significant increase in T2 lesion load compared to a previous MRI or at least one gadolinium-enhancing lesion, **AND** c) Two or more disabling relapses in the previous year. [18, 38]) Note: Must enroll in Tysabri Care program.[6]
Contraindic-ations	Hypersensitivity to *E. coli*-derived products, natural or recombinant interferon beta, human albumin or component of the formulation.[4]	Hypersensitivity to natural or recombinant interferons, human albumin or any other component of the formulation.[14]	Hypersensitivity to natural or recombinant interferons, human albumin, or any other component of the formulation.[4]	Hypersensitivity to Glatiramer acetate, Mannitol, or any component of the formulation.[4]	Hypersensitivity to Natalizumab, murine proteins, any component of the formulation History of PML.[4] Immunocompromised[5]
Lab Monitoring Parameters	- CBC and Liver function tests are recommended at baseline then once a month for 6 months then every 6 months thereafter.[19] -Thyroid function should be assessed at baseline and every 6 months in patients with history of thyroid dysfunction.[4]			No lab monitoring [4]	-Baseline and postinfusion gadolinium-enhanced MRIs (3 & 6 months, every 6 months thereafter). [4] -CSF analysis for JC viral

				DNA. [4] -Transient & reversible leukocytosis & mildly reduced hemoglobin may occur & can take 4 months to return to baseline.[4]

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Cost (these are approximates and can vary from pharmacy to pharmacy)	$19,000/year [20]	22 mcg: $18,000/year [20] 44 mcg: $22,000/year [20]	$17,000/year [20]	$16,000/year [20]	$34,000/year [20]
Coverage (SK)	-Apply through Saskatchewan Health using: MS Drugs Exception Drug Status Application, available at: www.health.gov.sk.ca -May be eligible for coverage through private and group health plans.[2] - A program called *Bridging the Gap* is available, call 1-800-977-2770. [2]	Apply through Saskatchewan Health using: MS Drugs Exception Drug Status Application, available at: www.health.gov.sk.ca -May be eligible for coverage through private and group health plans.[2] - *Multiple Support Program* is available, call 1-888-677-3243.[2]	Apply through Saskatchewan Health using: MS Drugs Exception Drug Status Application, available at: www.health.gov.sk.ca -May be eligible for coverage through private and group health plans.[2]	Apply through Saskatchewan Health using: MS Drugs Exception Drug Status Application, available at: www.health.gov.sk.ca -May be eligible for coverage through private and group health plans.[2] -*Copaxone Assistance Program* is available, contact shared solutions at 1-800-283-0034. [2]	Apply through Saskatchewan Health using: MS Drugs Exception Drug Status Application specific for Tysabri®, available at: www.health.gov.sk.ca -May be eligible for coverage through private and group health plans.[2] - Financial assistance may be available through *Canadian Tysabri Care Program.*[2]
Support Programs	BetaPlus (MS Pathways) 1-800-977-2770.	Multiple Support Program 1-888-677-3243.	Avonex Alliance 1-888-456-2263.	Shared Solutions 1-800-283-0034.	Tysabri Care Program 1-888-827-2827.
Pharmaceutical Company	Bayer HealthCare Pharmaceuticals[2]	EMD Serono Canada Inc. [2]	Biogen Idec Canada[2]	Teva Neuroscience [2]	Biogen Idec Canada [2]

Disease Modifying therapies are generally well tolerated but the potential for side effects exists.[6] Side effects are commonly experienced in the first few months of therapy and most will subside slowly thereafter.[6] The list of possible side effects below can be used to aid in selecting the appropriate medication, assist in determining whether an adverse event is caused by a medication, and if experiencing bothersome side effects can assist in the decision to consider a different option.

SIDE EFFECT COMPARISON CHART:	**Betaseron®** Interferon Beta 1b	**Rebif ®** Interferon Beta 1a	**Avonex®** Interferon Beta 1a	**Copaxone®** Glatiramer Acetate	**Tysabri®** Natalizumab
Flu Like symptoms (headache, fever, chills, malaise, diaphoresis, and myalgia)[4] – should decrease over time **Management:** Acetaminophen or Ibuprofen, injecting at bedtime, drinking lots of fluids.[6]	Common[4]	Common[14]	Common[4]	Infrequent[4]	
Post Injection reaction (tightness in chest, short of breath, anxiety, flushing, sweating and palpitations within a few hrs of injecting)[4] **Management:** This is temporary and does not require specific treatment.[6]				Infrequent[4]	
Cardiovascular: Chest Pain	Infrequent[4]	Rare[4]	Rare[4]	Infrequent[4]	Rare[4]
Peripheral Edema -accumulation of fluid in the peripheral[22]	Infrequent[4]			Rare[4]	Rare[4]
Facial Edema - accumulation of fluid in the face[22]				Rare[4]	
Vasodilation – increase in diameter of blood vessels[22]	Rare[4]	Rare[4]	Rare[4]	Infrequent[4]	
Palpitation – pounding or racing of the heart[22]	Rare[4]			Infrequent[4]	
Syncope – brief lapse of consciousness followed by light headedness[22]				Rare[4]	
Tachycardia – heart contracts at a rate greater than 100/min.[22]	Rare[4]			Rare[4]	
Central Nervous System: Headache (Try Tylenol)	Common[4]	Common[4]	Common[4]		Frequent[4]
Fever	Frequent[4]	Infrequent[4]	Infrequent[4]	Rare[4]	
Pain	Common[4]	Infrequent[4]	Infrequent[4]	Infrequent[4]	
Chills	Infrequent[4]	Infrequent[4]	Infrequent[4]	Rare[4]	
Dizziness	Infrequent[4]	Infrequent[4]	Infrequent[4]		
Insomnia – inability to sleep or remain asleep[22] (Try injecting earlier in the day)	Infrequent[4]				
Fatigue – state of exhaustion[22]		Frequent[4]	Frequent[4]		Infrequent[4]
Depression		Rare[14]	Infrequent[4]		Infrequent[4]
Anxiety	Infrequent[4]			Infrequent[4]	
Vertigo – sensation of instability and dizziness[22]				Rare[4]	Rare[4]
Malaise-vague feeling of weakness, distress, or discomfort[22]	Rare[4]	Rare[4]	Rare[4]		

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Dermatologic: Rash	Infrequent[4]	Rare[4]	Rare[4]	Infrequent[4]	Infrequent[4]
Skin Disorder	Infrequent[4]				
Pruritus – itching[22]				Infrequent[4]	Rare[4]
Bruising		Rare[4]	Rare[4]	Rare[4]	
Alopecia – loss of hair[22]	Rare[4]	Rare[4]	Rare[4]		
Dermatitis					Rare[4]
Lipoatrophy – loss of subcutaneous fat				Common[41]	
Endocrine and Metabolic: Thyroid Disorder	Rare[2]	Rare[14]	Rare[4]		
Dysmenorrhea – pain associated with menstruation[22]	Rare[4]			Rare[4]	Rare[4]
Metrorrhagia – uterine bleeding other than menstruation[22]	Infrequent[4]				
Amenorrhea – loss of menstrual period[22]					Rare[4]
Menstrual Disorder					Rare[4]
Gastrointestinal: Nausea	Infrequent[4]	Infrequent[4]	Infrequent[4]	Infrequent[4]	
Diarrhea	Infrequent[4]			Infrequent[4]	Infrequent[4]
Abdominal Pain	Infrequent[4]	Infrequent[4]	Infrequent[4]		Infrequent[4]
Constipation	Infrequent[4]				
Dyspepsia – feeling of fullness, heartburn, bloating & nausea[22]	Infrequent[4]				
Anorexia – loss of appetite[22]				Rare[4]	
Vomiting				Rare[4]	
Weight Gain (change)	Rare[4]			Rare[4]	Rare[4]
Genitourinary: Urinary Urgency	Infrequent[4]	Rare[4]	Rare[4]	Infrequent[4]	Rare[4]
Urinary Tract Infection		Infrequent[4]	Infrequent[4]		Infrequent[4]
Urinary Frequency	Rare[4]				Rare[4]
Impotence	Rare[4]				
Vaginitis					Infrequent[4]
Hematologic:					
Lymphopenia – decreased number of lymphocytes in blood[22]	Common[4]				
Neutropenia – decrease in number of neutrophils in blood[22]	Infrequent[4]				
Leukopenia – decrease in number of white blood cells[22]	Infrequent[4]	Frequent[4]	Frequent[4]		
Thrombocytopenia – reduction in the number of platelets[22]		Rare[4]	Rare[4]		
Anemia – decrease in hemoglobin in blood[22]		Rare[4]	Rare[4]		

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Hepatic: ALT increased (component of liver function test) AST increased (component of liver function test) Transaminases increased (component of liver function test)	 Infrequent[4] Rare[4]	 Infrequent[4] Infrequent[4]	 Infrequent[4] Infrequent[4]		 Rare[4]
Local: Injection site reaction Inflammation Pain Erythema – red/inflamed skin or mucous membrane[22] Pruritus – itching[22] Induration – hardening of the skin[22] Welt **Note:** Injection site reactions are more common with subcutaneous (Betaseron, Rebif, Copaxone), than intramuscular (Avonex) or intravenous (Tysabri) administration.[6] **Management:** These can be managed by rotating the site of injection, adjusting the depth of the autoinjector, or short term use of topical steroids.[6]	Common[4] Common[4] Infrequent[4]	Frequent[14] Rare[4]	Rare[4] Rare[4]	Common Frequent[4] Common[4] Common[4] Frequent[4] Infrequent[4] Infrequent[4]	Infrequent[4]
Neuromuscular and Skeletal: Weakness Myalgia – muscle pain[22] Hypertonia – increased muscle tone or strength[22] Myasthenia – abnormal weakness in muscles[22] Arthralgia – joint pain[22] Incoordination Back Pain Skeletal Pain Rigors – a ridged condition of the body tissues[22] Neck Pain Tremor Extremity Pain	Common[4] Infrequent[4] Common[4] Frequent[4] Frequent[4] Infrequent[4]	Infrequent[4] Infrequent[4] Rare[4] Rare[4] Rare[4] Infrequent[4] Infrequent[4] Rare[4]	Infrequent[4] Infrequent[4] Rare[4] Rare[4] Rare[4] Infrequent[4] Infrequent[4] Rare[4]	Frequent[4] Infrequent[4] Infrequent[4] Infrequent[4] Rare[4] Rare[4]	 Infrequent[4] Rare[4] Rare[4] Infrequent[4]
Ocular: Vision Abnormal		Infrequent[4]	Infrequent[4]	Rare[4]	

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Respiratory: Sinusitis– inflammation of the sinuses[22]		Infrequent[4]	Infrequent[4]		
Upper Respiratory Tract Infection		Infrequent[4]	Infrequent[4]		
Dyspnea – shortness of breath [22]	Rare[4]			Infrequent[4]	
Rhinitis – inflammation of mucous membrane in the nose[22]				Infrequent[4]	
Bronchitis – inflammation in the bronchioles[22]		Rare[4]	Rare[4]		
Lower Respiratory Infection					Infrequent[4]
Tonsillitis					Rare[4]
Miscellaneous:					
Antibodies (please see section on this for significance)	Frequent[23]	Infrequent[23]	Rare[23]	Common[12]	Rare[5]
Lymphadenopathy – enlargement of the lymph nodes[22]	Rare[4]	Infrequent[4]	Infrequent[4]	Infrequent[4]	
Infection		Rare[4]	Rare[4]	Common[4]	Rare[4]
Diaphoresis – profuse secretion of sweat[22]	Rare[4]			Infrequent[4]	
Tooth infection					Rare[4]
Herpes					Rare[4]
Hypersensitivity Reaction					Rare[4]

Rare: < 10%
Infrequent: 10%-29%
Frequent: 30%-50%
Common: >50%

Treatment Options:

Primary Treatment:
Beta Interferons: Betaseron®, Rebif®, Avonex®
Glatiramer Acetate: Copaxone®
Secondary Treatment:
Monoclonal Antibody: Tysabri®

Combination Therapy:

- Currently no combinations are approved or recommended.

Treatment of Relapses with Glucocorticoids:

	IV Pulse Therapy: Methylprednisolone	Oral: Prednisone
Doses:	1 g each day for 3 to 5 days (can be followed by an oral prednisone taper).[24,25] Methylprednisolone equivalence = 4 (for dose conversions)	1250 mg on alternate or daily dose schedules of 3 to 5 days.[24,25] Prednisone equivalence = 5 (for dose conversions)
When to treat:	Consider Glucocorticoid treatment for any patient with an acute attack of MS.[7]	
What to expect from the medications:	Short term benefits are seen on the speed of recovery in patients experiencing an acute MS attack (no known long term benefits seen).[7] The oral route has been shown to be as safe and effective as the intravenous route.[24]	
Common side effects:	Note: Short term high dose oral prednisone does not seem to be associated with more gastric damage than IV methylprednisolone.[25] Short Term Side Effects: metallic taste, facial flushing, altered appetite, weight gain, stomach upset, restlessness, mood swings, insomnia, fluid retention, and glucose intolerance (small chance of psychosis; monitor).[4] Long Term Side Effects: cataract formation, GI bleeding, osteoporosis.[4] All patients who have received steroid treatment for relapses should be followed on an ongoing basis for potential long-term side effects.	

Uncommonly Used Medications:

	Proposed Mechanism of Action	Effectiveness:
Novantrone® (Mitoxantrone) → Approved in the US but not in Canada for the treatment of worsening RRMS or SPMS. [26] → Health Canada has not specifically approved Novantrone for MS, but it can be used at the discretion of the physician for the above indications as "off-label" use.[26]	- Chemotherapeutic Agent (anti-cancer) [27] -Impairs the immune system in a variety of ways [27] - Suppresses the number and activity of white blood cells that induce the MS attack in the CNS.[6]	→ Probably reduces the attack rate in patients with relapsing forms of MS.[7] The potential toxicity of mitoxantrone may outweigh the clinical benefits early in the disease course. [7] → Mitoxantrone may have a beneficial effect on disease progression in MS, although this clinical benefit has not been proven. [7] **Dose:** 12 mg/m^2 every 3 months (max lifetime cumulative dose: 140 mg/m^2)[4] Given by intravenous infusion over 5-30 minutes (into the vein). [4] -Must be reconstituted prior to use (dilute in at least 50 mL of NS or D5W) [4] **Storage:** Store intact vials at 15-25ºC; do not freeze. Opened vials may be stored at room temp. for 7 days or refrigerated for 14 days. Solutions diluted are stable for 7 days at room temp. or refrigerated.[4] **Common Side Effects:** Nausea/upset stomach, hair thinning, loss of menstrual period, bladder infections, changes in heart beat, low white blood cell counts, and mouth sores.[4] **Lab Monitoring:** CBC, Liver function tests, signs and symptoms of CHF, evaluate LVEF prior to start of therapy and prior to each dose. [4] **Warnings:** -Do not use if baseline neutrophil count <1500 cells/mm^3.[4] -May cause myocardial toxicity & CHF; risk increases with cumulative dosing.[4] -Do not use in patients with hepatic impairment, or if LVEF <50% or significant ↓ in LVEF.[4] **Pregnancy and Lactation**: Pregnancy Risk Factor D, excretion in breast milk is significant. [4]
Azathioprine	- Chemotherapeutic Agent (anti-cancer) [27] -Impairs the immune system in a variety of ways [27]	- Possibly reduces relapse rates, but its effect on disability progression has not been demonstrated[7]
Cyclophosphamide	- Chemotherapeutic Agent (anti-cancer) [27] -Impairs the immune system in a variety of ways[27]	- Pulse Cyclophosphamide treatment does not seem to alter the course of progressive MS[7] - Younger patients with progressive MS may have some benefit from pulse plus booster Cyclophosphamide treatment[7]
Cyclosporine	- Chemotherapeutic Agent (anti-cancer) [27] -Impairs the immune system in a variety of ways[27]	- Possibly provides some therapeutic benefit in progressive MS, but the frequent occurrence of adverse reactions (nephrotoxicity), along with its small potential for benefit makes this therapeutic approach unacceptable. [7]

Methotrexate	- Chemotherapeutic Agent (anti-cancer) [27] -Impairs the immune system in a variety of ways [27]	- Possibly it favorably alters the disease course in patients with progressive MS[7]
IV Immunoglobulin	Decreases the severity of viral infections and may reduce severity of relapses[27]	- IV immunoglobulin possibly reduces the attack rate in RRMS[7] - Current evidence suggests little benefit with regard to slowing of the disease[7]
Cannabinoids	- Blocks receptors in the brain that cause the patient to feel pain and/or experience muscle spasms[28] - Stimulates cannabinoid receptors in the CNS inducing analgesia[4]	- Approved in Canada in 2005 as an adjunctive treatment for neuropathic pain in MS patients[28] - Patients followed for 12 months from the CAMS study showed evidence of a small effect on muscle spasticity, suggestive evidence for some aspects of disability and no major safety concerns were noted.[29]

Experimental Medications:

Cladribine	- Chemotherapeutic Agent (anti-cancer) [27] -Impairs the immune system in a variety of ways[27]	- Reduces Gd enhancement in patients with both relapsing and progressive forms of MS; however it does not appear to favorably alter the disease course. [7]
Alemtuzumab	Monoclonal antibody that kills T-cells[27]	Current Study: interim results from the CAMMS223 Phase 2 study (2 years into a 3 year study) show a once-yearly cycle of Alemtuzumab treatment had a statistically significant impact on reducing the frequency of relapses and the sustained accumulation of disability in early active RRMS patients compared to Rebif®.[30] Alemtuzumab at the high dose resulted in an 87% reduction in the risk for relapse and a 66% reduction in the risk for progression of clinically significant disability compared to Rebif® treated patients.[30] Patients taking Alemtuzumab at the low dose had a 72% reduction in the risk for relapse and an 88% reduction in the risk for progression of clinically significant disability compared to Rebif® treated patients. [30] Patients in both Alemtuzumab arms also achieved a statistically significant reduction in disability compared with their pre-treatment baseline, as measured by EDSS scores.[30]
4-Aminopyridine and 3, 4-Diaminopyridine	Blocks potassium channels in neurons which may improve nerve transmission in MS[27]	Pharmacologic agents that block potassium channels have been found to improve conduction in experimentally induced demyelination, and produce symptomatic improvement in some MS patients. [31] Toxicity, particularly seizures, has limited the use of the 2 available agents in MS patients. Ongoing research is further defining the molecular pharmacology of both the improvements seen in patients and seizures and other toxicities.[31]
Eliprodil	Might promote remyelination[27]	- Potential benefits in MS[32]
Minocycline	Believed to work by inhibiting an enzyme that initiates inflammation in the brain in MS[33]	- An 84% reduction in MS lesion activity on brain MRI was seen in early studies; however more research is currently being done. [33]
Statins	- Reduces inflammation that causes nerve cell damage by inhibiting the formation of lymphocytes and monocytes, may also have immunomodulatory properties [28]	- Has been shown in patients that take statins that they have fewer relapses and lesion formation than those not taking statins. [28]

Deciding on a Treatment:

As seen on an MRI, plaques can appear with each relapse, and developing irreversible impairment and disability over time is a risk[21]. Hence, initiation of therapy is advised as soon as possible following a definite diagnosis of MS and determination of a relapsing course.[34] Therapy is to be continued indefinitely, unless a demonstrated clear lack of benefit, intolerable side effects, new data that reveal other reasons for cessation, or better therapy becomes available. [34]

When deciding on a treatment, the following considerations are important:

- Route of administration
- Frequency of administration
- Side effects of the different medications
- Contraindications of the medications
- Warnings and precautions of the medications
- Preparation and storage of the medications

All of this information is profiled in the charts above. This information has different importance to each individual and medication must be chosen on an individual basis.

Switching/Discontinuing Treatments:

Criteria for Discontinuing Medication (any one or more of the following):

- Is not able to walk for 100 meters without aids or assistance[35] (This is a sign of worsening disease and the available medications have not been approved for this use)
- Pregnancy[35]
- Concurrent illness likely to substantially reduce life expectancy, or cause compliance issues[35]

Criteria for Switching Medication (any one or more of the following):

- Exacerbations while on drug therapy have continued[35]
- Steady disability progression over the past year[35]
- Treatment with at least 3 courses of ACTH, corticosteroids or pulse therapy within a one year period[35]
- Consistent noncompliance in taking the medication as prescribed[35]
- Severe drug toxicity.[35] Note: Health Canada advices either dose reduction or discontinuation of beta interferon therapy be considered if alanine aminotransferase (ALT) levels increase to five times above the upper limit of normal.[19]

If the patient finds the side effects of the medication unacceptable, or taking the drug becomes inconvenient, they should discuss changing to another medication with their neurologist. It is important to understand that treatment is not ineffective just because a relapse is experienced.

Resources for further information:

MS society of Canada: www.mssociety.ca
MS society of Canada: Saskatchewan Division: www.mssociety.ca/sask/services.htm
National MS society: www.nationalmssociety.org
The MS Information Sourcebook, produced by the National MS Society:
http://www.nationalmssociety.org/site/PageServer?pagename=HOM_LIB_sourcebook
Betaseron Home Page: www.betaseron.com
Rebif Home Page: www.rebif.com
Avonex Home Page: www.avonex.com
Copaxone Home Page: www.copaxone.com
Tysabri Home Page: www.Tysabri.com

List of Terms and Abbreviations:

Abortifacient- An agent that causes termination of pregnancy before the fetus has developed to a stage of viability.[22]
ACTH- Adrenocorticotropic Hormone; an anterior pituitary hormone that stimulates the adrenal cortex to secrete cortisol, aldosterone, and other substances. [36] Increased secretion of these natural steroids provides an anti-inflammatory and immunosuppressive effect to speed up recovery from an MS exacerbation or attack. [36] It is used to treat MS relapses, but glucocorticoids such as prednisone are considered as first line, and then ACTH would be another option.[36]
Albumin- A protein found in all animal tissues [22]
Anemia- A decrease in hemoglobin in the blood to levels below the normal range. [22] Can be caused by a decrease in red cell production, an increase in red cell destruction, or a loss of blood. [22]
Angina- A condition where chest pain occurs due to lack of oxygen to the heart. [22]
Antibody- An immunoglobulin produced by lymphocytes in response to bacteria, viruses, or other antigenic substances. [22]
Anticoagulant- Prevents or delays clotting of the blood [22]
Antigen- A substance that the body recognizes as foreign and evokes an immune response [22]
Antiviral- Destructive to viruses [22]
Arrhythmia- Any deviation from the normal pattern of the heartbeat [22]
Cardiomyopathy- Any disease of the heart muscle causing enlargement [22]
Cardiovascular- Pertaining to the heart and blood vessels [22]
CBC- Complete Blood Count; a determination of the number of red and white blood cells in the blood. [22]
CDMS- Clinically Definite Multiple Sclerosis
CHF- Congestive Heart Failure; a condition where the heart pumps abnormally[22]
CIS- Clinically Isolated Syndrome; or single event suggesting MS. [2]

CNS-Central Nervous System, including the brain and spinal cord[22]
CSF analysis- Cerebral Spinal Fluid analysis; a lumbar puncture is used to gather the fluid for examination. [22]
Cytokines- Proteins involved in cell to cell communication, coordinating antibody and T cell immune interactions, and amplifying immune reactivity. Interferons are cytokines. [22]
DNA- Deoxyribonucleotide
EDSS- Extended Disability Status Scale;[30] a standardized rating scale used by clinicians as well as researchers
Enzyme- A complex produced by living cells that catalyzes chemical reactions within the body [22]
Exacerbation- An increase in the seriousness of MS marked by greater intensity in signs and symptoms. [22]
Fibroblasts- A cell in the connective tissue which forms the fibrous, binding, and supporting tissue of the body. [22]
Gadolinium or Gd- A contrast agent used in MRIs [22]
Gastric- Pertaining to the stomach [22]
GI- Gastrointestinal; pertaining to the organs of the GI tract, from mouth to anus. [22]
Glucocorticoids- Exerts an anti-inflammatory effect [22]
Glycosylation- The formation of linkages with saccharides such as glucose.[22]
Granulocytopenia- An abnormal decrease in the number of granulocytes (a type of leukocyte) in the blood. [22]
Half Life- The time required for a substance to lose 50% of its activity [22]
Hemoglobin- A protein iron compound in the blood that carries oxygen to the cells in the body. [22]
Hepatic- Pertaining to the liver[22]
Hypersensitivity Reaction- An inappropriate and excessive response of the immune system to a sensitizing antigen called an allergen. [22]
IgG- Immunoglobulin G [22]
Immune System- A system of tissues and organs that protects the body against pathogenic organisms and other foreign bodies.[22]
Immunocompromised- A weakened immune response [22]
Immunoglobulin- A protein that functions as an antibody [22]
Immunomodulatory- Alters the immune response by augmenting or reducing its ability to produce antibodies.[22]
Immunosuppressant- An agent that lessons or prevents the immune response [22]
Integrin- A protein that links the outside of a cell with the tissues/cells surrounding it.[22]
Interferon Beta- Occurs naturally in the human body in response to initiating factors such as viruses.[2]
JC Virus- A polyomavirus that causes widespread infection in childhood and remains latent in the host; it is the cause of progressive multifocal leukoencephalopathy.[36]
Leukocyte- White blood cell [22]
Leukocytosis- An abnormal increase in the number of white blood cells [22]
Liver function test- A test used to evaluate various functions of the liver (blood test) [22]
LVEF- Left ventricle ejection fraction; a test used as a sign of worsening heart failure, which shows the contractile force of the heart. [22]
Mannitol- A poorly metabolized sugar used in kidney function tests and in many drug formulations[22]

Monoclonal Antibody- An antibody produced in the laboratory from a single clone, producing identical clones with the same antigenic specificity. [22]
Monotherapy- Treatment using a single agent [22]
MRI- Magnetic Resonance Imaging; a tool that provides images of the brain, spinal cord, or other areas of the body. [2] Used in MS to identify areas of inflammation.[2]
Myelin- The insulation material that protects nerves and helps them function properly. [2]
Myocardial – Contractile layer forming the bulk of the heart wall [22]
Neutralizing Antibodies- An antibody that reacts with the interferons to inhibit their effect.[36]
Neutrophil- Circulating white blood cells [22]
Plaque (sclerosis)- Abnormal hardening of tissue caused by inflammation. [22]
Platelet- The smallest cells in the blood, which are responsible for clotting [22]
PML- Progressive Multifocal Leukoencephalopathy; a rare brain disease caused by the JC-virus that can potentially cause severe disability or death. [2]
Potassium Channels- They shape action potentials in excitable cells such as neurons. [36]
Prefilled Syringe- Ready for injection; no mixing involved.
Reconstitution- Must be mixed prior to use
Relapse- A period of over 24 hrs characterized by increased symptoms or the appearance of new symptoms also called an attack or flare-up.[1]
Remission- The period after a relapse when symptoms subside [22]
Renal- Pertaining to the kidney [22]
Respiratory- Pertaining to breathing [22]
RRMS- Relapsing Remitting Multiple Sclerosis; characterized by recurrent attacks followed by complete or incomplete recovery.[2]
Spasticity- Spasticity refers to feelings of stiffness and involuntary muscle spasms. Spasticity may be mild; feeling of tightness of muscles, or may be severe; as to produce painful, uncontrollable spasms of extremities, usually of the legs.[1]
SPMS- Secondary Progressive Multiple Sclerosis; a form of MS in which the symptoms become progressively and steadily worse over time. May include periods of acute deterioration in patients with RRMS[36]
T-Cells or T-Lymphocytes- A white blood cell that mediates immune responses in the body.[22]
T½ - see half life

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