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Key Inforbits

- What is Multiple Sclerosis?
- Who does MS affect?
- What are the Risk Factors and Causes of MS?
- What are the Main Symptoms?
- How is MS Treated
- New Drug: fingolimod (Gilenya®)
- New Drug: Laquinimod
- New Drug: BG-12

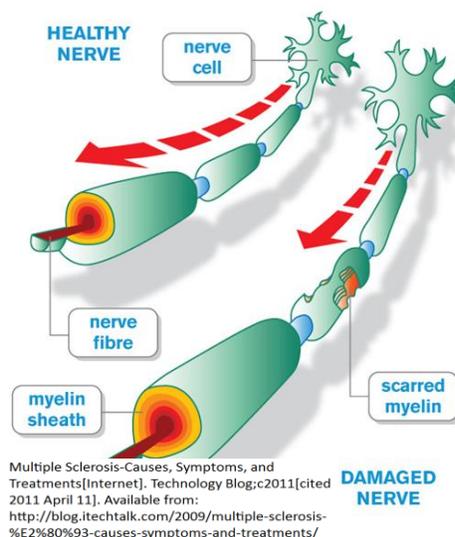


May is Multiple Sclerosis Awareness Month!

What is Multiple Sclerosis (MS)?

MS is a chronic central nervous system (CNS) disease that affects the brain, optic nerves and spinal cord.¹ The myelin sheath is stripped away producing lesions, which leads to blockage or slower message transduction between the brain and the body.² Specific time of progression, severity and symptoms of MS are all unpredictable from one person to another. New advances in research, early treatments, and alternative healing options are giving hope to people affected with MS.³

1. Saseen JJ, MacLaughlin EJ. Multiple Sclerosis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: A pathophysiologic approach*. 7thed. New York: McGraw-Hill Medical; c2008. p. 913-25.
2. What is Multiple Sclerosis [Internet]. Multiple Sclerosis Foundation. c2009 [cited Apr 2011]. Available from: <http://www.msfocus.org/what-is-multiple-sclerosis.aspx>
3. What is MS [Internet]. New York: National Multiple Sclerosis Society; [cited 2011 Apr 11]. Available from: <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-causes-ms/index.aspx>



Who Does MS affect?

MS can affect anyone and about 400,000 people are suffering currently in the United States.¹ There are about 200 new cases diagnosed every week. It is approximated that MS affects about 2.1 million people worldwide. MS is about 2-3 times more common in women than men and most people are diagnosed between the ages of 20 and 50. MS has occurred in most ethnicities but is most common in Caucasians of northern European origin. This trend is thought to be due to the distance from the equator and lack of Vitamin D.

1. Who gets MS? [Internet]. New York: National Multiple Sclerosis Society; [cited 2011 April 11]. Available from: <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx>

What are the main symptoms?

Most common symptoms include fatigue (up to 78%), weakness, spasticity (stiff or rigid muscles with exaggerated reflexes of deep tendons; 41%-62%), balance problems, visual disturbances, vertigo, tingling or numbness (up to 55%), cognitive impairments, depression, sexual difficulties (changes sexual sensation drive and interest: 90% men; 70% women) and tremor.¹ It's important to understand that not all symptoms will affect each patient with MS. Symptoms often present in cycles with episodes of attack and remission throughout the chronic disease. More specifically, the symptoms that define the clinical version of MS,

depends on location of the nerve lesions. The following chart depicts, some of the signs or symptoms associated with MS lesion location.²

Lesion Location ²	Signs/Symptoms ²
Cerebrum & Cerebellum	Balance problems, speech problems, coordination, tremors
Motor Nerve Tracts	Muscle weakness, spasticity, paralysis, vision, bladder, bowel problems
Sensory Nerve Tract	Altered sensation, numbness, prickling, burning sensation

1. Saseen JJ, MacLaughlin EJ. Multiple Sclerosis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 7thed. New York: McGraw-Hill Medical; c2008. p. 913-25.
2. Symptoms of Multiple Sclerosis [Internet]. Multiple Sclerosis Foundation. c2009 [cited Apr 2011]. Available from: <http://www.msfocus.org/what-is-multiple-sclerosis.aspx>

What are the Risk Factors and Causes of MS?

The cause of MS is unknown, but is thought to be due to multiple factors. Most commonly these factors are thought to be immunologic, environmental, infectious, and genetic.¹ Although the exact antigen is still a mystery, researchers have begun to make medications that modulate specific immune cells that help to prevent the destruction of the myelin. Some scientists believe that people closer to the equator are at a lower risk of developing MS. This is due to the increased amount of Vitamin D that is naturally produced by this population. Vitamin D is believed to provide protection against autoimmune diseases. Viruses and bacteria are known to cause demyelination and inflammation. Measles, canine distemper virus, human herpes virus-6, Epstein-barr, and Chlamydia pneumonia are being investigated to determine if they are possible causes of MS. MS is not hereditary, but a person is at higher risk of developing MS if a first degree relative is suffering from MS. There is a 5% chance of another family member developing MS and this is especially seen in siblings.

1. What causes MS?[Internet]. New York: National Multiple Sclerosis Society;[cited 2011 April 11]. Available from: <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-causes-ms/index.aspx>

Therapy

Exacerbation Treatment...usually treated with high dose corticosteroids to decrease the inflammation in the CNS.¹ Intravenous and oral methylprednisolone is used commonly at doses ranging from 500 to 1,000 mg/day for variable durations of 3 to 10 days.² Improvement usually occurs in 3 to 5 days. For severe attacks that may cause paralysis plasma exchange every other day for 7 treatments has been effective in patients unresponsive to corticosteroids.

1. Treatment [Internet]. New York: National Multiple Sclerosis Society;[cited 2011 April 11]. Available from: <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/index.aspx>
2. Saseen JJ, MacLaughlin EJ. Multiple Sclerosis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 7thed. New York: McGraw-Hill Medical; c2008. p. 913-25.

Modifying the disease...Decrease disease activity and slow progression of the disease.

Beta Interferons modulate the activity of the lymphocytes and macrophages which help to decrease inflammation and slow the progression of destruction.¹ Interferon β1b (Betaseron[®] and Extavia[®]) is a synthetic analog of interferon-β and is produced by E-coli. This medication is injected subcutaneously every other day at a target dose of 0.25 mg. Betaseron[®] and Extavia[®] cost approximately \$35,000 per year.² Interferon β1a (Avonex[®] and Rebif[®]) are natural interferon produced by Chinese hamsters. Avonex[®] is given intramuscularly once weekly at a dose of 30 mcg and Rebif[®] is given as either 22 or 44 mcg subcutaneously three times weekly. These medications cost approximately \$36,000 per year.² Most common ADRs include injection site redness, swelling, and flu-like symptoms.³ These flu-like symptoms usually subside after 1 to 3 months of therapy.¹

1. Saseen JJ, MacLaughlin EJ. Multiple Sclerosis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 7thed. New York: McGraw-Hill Medical; c2008. p. 913-25.
2. Betaseron, Extavia, Avonex, Rebif[Internet]. Drug Store.com;c2011[cited 2011 April 11]. Available from: <http://www.drugstore.com>
3. Interferon β1b, Interferon β1a. In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc.[updated 2011, cited 2011 April 11]. Available from:<http://online.lexi.com/crlsql/servlet/crlonline>

Glatiramer acetate (Copaxone[®]) is a synthetic analog of MBP (myelin basic protein) which prohibits the binding of natural MBP to prevent destruction of the myelin.¹ Glatiramer is given 20 mg subcutaneously once daily and costs approximately \$45,000 per year.^{2,3} It is currently approved in US to prevent MS

relapses. Most common ADRs include mild pain and injection site reaction. Patients also may experience a one-time reaction of chest tightness, flushing, and shortness of breath that subsides after about 20 minutes.³

1. Review article
2. Copaxone[Internet]. Drug Store.com;c2011[cited 2011 April 11]. Available from: <http://www.drugstore.com>
3. Copaxone. In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc.[updated 2011, cited 2011 April 11].Available from:<http://online.lexi.com/crlsql/servlet/crlonline>

Natalizumab (Tysabri®) is humanized monoclonal antibody that blocks the attachment of $\alpha_4\beta$ -integrin (VLA-1) from binding to its ligand.¹ This prohibits lymphocytes from moving across blood brain barrier which leads to decreased lesion production. Natalizumab is approved as monotherapy at a dose of 300 mg every 4 weeks as an infusion over 1 hour. The approximate cost for a year supply is \$36,000, but this medication needs to be administered in a physician's office so this could add an additional cost.² Tysabri® was pulled from the market in 2005 due to cases of progressive multifocal leukoencephalopathy (PML: a rare brain infection). It was relaunched in 2006 with strict monitoring regulations and a black box warning.¹ In March of 2011 a new label was released which updated the incidence of progressive multifocal leukoencephalopathy (PML: a rare brain infection) The FDA continues to support the use Tysabri® since the clinical benefits have shown to outweigh the risks.³

1. Saseen JJ, MacLaughlin EJ. Multiple Sclerosis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 7thed. New York: McGraw-Hill Medical; c2008. p. 913-25.
2. Tysabri FAQs[Internet]. Biogen Idec and Elan Pharmaceuticals, Inc. c2009;[cited 2011 April 12]. Available from: http://www.tysabri.com/tysbProject/tysb.portal/_baseurl/threeColLayout/SCSRepository/en_US/tysb/home/about-tysabri/tysabri-faqs.xml
3. Gryta T. Biogen, Elan's Tysabri Label Updated. The Wall Street Journal. 2011 Apr 7:Sect. Health Industry

Mitoxatrone (Novantrone®) is an antineoplastic agent that has also been used in treatment of multiple cancers. In MS it suppresses the actions of T cells, B cells, and macrophages to decrease destruction of the myelin sheath.¹ Based on European studies the FDA approved the mitoxatrone use at a dose of 12 mg/m² for 8 to 12 doses divided into 2 to 3 years in normal cardiac patients. The lifetime cumulative dose is 140 mg/m². The FDA added a black box warning due to the cardiotoxicity. Prior to the start of treatment every patient should be evaluated for heart disease and any patient with LVEF <50% should not be given this medication. Other ADRs include nausea, hair loss, upper respiratory tract infection and development of AML (Acute Myeloid Leukemia)² The approximate cost for 12 doses is \$19,000.³

1. Novantrone(mitoxantrone)[Internet]. New York: National Multiple Sclerosis Society;[cited 2011 April 12]. Available from: <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/medications/mitoxantrone/index.aspx>
2. Saseen JJ, MacLaughlin EJ. Multiple Sclerosis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 7thed. New York: McGraw-Hill Medical; c2008. p. 913-25.
3. Novantrone. Red Book .Pharmacy's Fundamental Reference. 2010 edition. [cited 2011 Apr 13]. p618

New Drug...fingolimod (Gilenya®) 0.5 mg has been approved for patients with relapsing-remitting MS. This is the first oral medication approved in the U.S. and has showed to be as effective in preventing relapse as one of the most common treatments, interferon-beta 1a.¹ Fingolimod helps prevent autoaggressive lymphocyte movement to decrease inflammation and lesion formation. In order for a patient to begin this therapy, their physician must request the medication from Novartis and the medication must be administered in the physician's office due to bradycardia that presents after the first dose of medication.² Other common ADRs include upper respiratory tract infections, dyspnea, headache, diarrhea and nausea.³ Patients should be cautioned if they have a history of cancer, heart conditions, macular edema, and infection due to increased occurrence of these side effects with the administration of fingolimod. A disadvantage of this new medication is price. According to Novartis the current AWP is \$4500.00 per month.² There are assistance programs that patients may apply for to help with the cost of this medication.⁴

1. Cohen JA, et al.Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis. N Engl J Med. 2010 Feb 4; 362: 402-415.
2. Personal Communication: Novartis Pharmaceuticals Corp., Dr. Info, Medical Information Dept., Cassandra.,877-408-4974, March 30, 2011.
3. Fingolimod. In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc.[updated 2011, cited 2011 April 11].Available from:<http://online.lexi.com/crlsql/servlet/crlonline>
4. CMSC Informs: Novartis on Gilenya Support Programs [Internet]. The Consortium of Multiple Sclerosis Centers;c2010[cited 2011 April 11];[about 1 screen]. Available from: http://mscare.org/cmssc/index.php?option=com_content&task=view&id=1076&Itemid=1465

New Drug...Laquinimod, an investigational oral immunomodulator, that recently (2011 Jan) completed a two-year double-blind phase III placebo-controlled trial, evaluating it's efficacy in treatment of relapsing-remitting multiple sclerosis (RRMS).¹ The trial hasn't been published yet, but an abstract was just released, indicating laquinimod's efficacy in reduction of the disease progression and relapse rate. Laquinimod's

proposed mechanism of action is to shift lymphocytes to H2/Th3 cytokine profiles, which limits the amount of leukocytes into the CNS causing less destruction to the myelin sheaths.² Previously a phase II trial demonstrated laquinimod's safety profile which was well tolerated with MS patients.

1. Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety and Efficacy of Daily Oral Administration of Laquinimod 0.6 mg in Subjects With Relapsing Remitting Multiple Sclerosis (RRMS) ClinicalTrials.gov. c2011 [updated 2011 Jan 13, cited 2011 Apr 13] Available from: <http://clinicaltrials.gov/ct2/show/NCT00509145>
2. Bagert BA, Bourdette D. New oral disease-modifying therapies for multiple sclerosis. *Medicine Reports*. 2009;1(34):1-4.

New Drug...BG-12 is a new oral dimethyl fumarate medication currently studied to treat relapsing-remitting MS. This medication is thought to interfere with oxidative stress, protect the blood brain barrier, and decrease the inflammatory response which helps to prevent destruction of the myelin. In a phase II, 257 patients with diagnosed relapsing-remitting MS were given either BG-12 120 mg daily, 120 mg three times daily, 240 mg three times daily, or placebo. The patients receiving BG-12, 240 mg three times daily showed significantly fewer new lesions compared to placebo. The other experimental groups did not show a significant difference. The annualized relapse rate did not differ among the 4 groups. The most common ADRs reported were flushing, MS relapse, and headache. Phase III trials are in progress to further identify BG-12's role in the treatment of MS. If relapse rate reductions are proven to be similar to therapies already in use for MS then this drug maybe suitable for treatment and especially for those unable to use injection therapy.

1. Kappos L, Gold R, et al. Efficacy and safety of oral fumarate in patient with relapsing-remitting multiple sclerosis: a multicentre, randomized, double-blind, placebo-controlled phase IIb study. *Lancet*. 2008 Oct 25;372:1463-1472.

Frequently Asked Questions About MS?

- Is MS contagious or fatal? **No, it's not fatal or contagious.**
- Why do doctors feel that patients imagine their symptoms? **Certain diagnostic tests, like MRI's may show negative results, and many of the symptoms (tingling, numbness, or fatigue) are subjective, which can't be viewed with diagnostic tests. Clinical diagnosis can take years to confirm depending on progression of MS, and expertise of the diagnosing physician.**
- Do all people with MS, end up in a wheelchair? **Not necessarily, about 75% of people with MS get around without wheelchairs. Early diagnosis, early treatment, and consistent evaluation with an MS healthcare team will provide the best results.**
- Does stress affect multiple sclerosis? **No, it simply helps to have a healthy mental status to effectively live with MS, and it's many complications.**
- Can women with MS get pregnant? **Yes, MS does not physically inhibit women from getting pregnant and carrying a child to full term.**

1. Multiple Sclerosis FAQs [Internet]. Multiple Sclerosis Foundation. c2009 [cited Apr 2011]. Available from: <http://www.msfocus.org/multiple-sclerosis-faqs.aspx>
2. Frequently Asked Questions About Multiple Sclerosis. [Internet] c2011 [cited Apr 2011]. Available from: <http://www.webmd.com/multiple-sclerosis/guide/multiple-sclerosis-faq>



The last "dose" ...

"Philosophy, like medicine, has plenty of drugs, few good remedies, and hardly any specific cures."

Sébastien-Roch Nicolas De Chamfort, French Playwright (1741-1794)



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