DEVELOPMENT

March 19, 2010	**CC:** Chapter Presidents
2009 Top Teams / Top Fundraisers Lists available	

We are pleased to announce that the finalized lists of 2009 Top Teams and Top Fundraisers are now available both on SharePoint (under Development, in the appropriate event section) and on the national website under the Bike MS, Walk MS and Challenge Walk event pages.

These lists are a great reminder of the incredible fundraising work of our participants and teams, and will hopefully be a source of pride for those who made the list, and a source of motivation for those who didn't! Congratulations to all of our development staff for cultivating these tremendous fundraisers!

Please contact sarah.klein@nmss.org with any questions.

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RESEARCH/CLINICAL UPDATE

	cc: Chapter President, Programs

March 12, 2010

FDA Approves Botox® for Treating Spasticity, or Tightness, in Upper Limbs

A new use for Botox® (onabotulinumtoxin A, Allergan, Inc.) was approved by the U.S. Food and Drug Administration, providing an additional treatment option for people with MS or other disorders who may experience spasticity in muscles of the elbow, wrist and fingers. Spasticity is an often painful muscle tightness that can make movements difficult. In clinical trials largely involving people with spasticity after stroke, targeted injections of Botox into muscles were found to be beneficial and safe.

Background: Botox is a powerful neurotoxin that temporarily blocks connections between the nerves and muscles, resulting in short-term relaxation of the targeted muscle. Injections have been shown in clinical trials to relieve spasticity in individual muscles for up to three months. For many years some doctors have injected Botox directly into overactive muscles in people with MS-related spasticity who did not get relief from the first-line oral medications such as baclofen and tizanidine. While the oral medications continue to be the most effective strategy to manage generalized spasticity of the upper and lower limbs, having Botox specifically approved for treating upper limb spasticity adds a welcome strategy and paves the way for its reimbursement by health insurers. Botox is also being tested in MS for its usefulness in the management of certain types of urinary symptoms.

FDA Approval: Botox is a well-studied drug that is now approved for five different indications in the U.S. According to a company press release, the FDA approval for treating upper spasticity was based on results of three double-blind, placebo-controlled studies, two of which were published, involving people who had upper-limb spasticity after stroke. (Arch Phys Med Rehabil. 2004 Jul;85(7):1063-9. http://www.ncbi.nlm.nih.gov/pubmed/15241751; N Engl J Med. 2002 Aug 8;347(6):395-400. http://www.ncbi.nlm.nih.gov/pubmed/12167681). The studies showed benefit over placebo in treating upper limb spasticity.

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According to the approved label, the dosing regimen should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, presence of local muscle weakness, the patient's response to previous treatment, or adverse event history. Generally it can be given every 12 weeks.

The most common adverse events included pain in the arms, fatigue, muscle weakness, nausea and bronchitis. According to the label, it is not known whether Botox is safe or effective in treating spasticity in children younger than 18. The medication carries a boxed warning that Botox injections may cause serious side effects that can be life threatening. These include problems swallowing, speaking or breathing, and the possibility that the toxin may spread to other areas of the body away from the injection site.

Comment: "The FDA's approval of Botox for the treatment of upper-limb spasticity addresses an important and often painful symptom for many people with MS, and as such is a welcome addition to strategies available for treating spasticity," commented Aaron Miller, MD, Chief Medical Officer for the National Multiple Sclerosis Society and Director of Clinical Affairs at the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at Mount Sinai Medical Center in New York City.

If you have questions about the use of Botox for the treatment of spasticity, please consult your healthcare provider.

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Botox is a registered trademark of Allergan, Inc.

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Surprising Phase II Clinical Trial Results of Oral Ibudilast Show Some Evidence of Neuroprotection But Little Impact Against Inflammation in MS

Ibudilast (previously known as MN-166, Medicinova, Inc.), an oral anti-inflammatory agent, did not reduce relapses or MRI-observed inflammation in a phase II study of 292 people with relapsing MS. However, some evidence that this agent could protect the nervous system from damage (neuroprotection) was observed in this study. Frederick Barkhof, MD, PhD (VU University Medical Center, Amsterdam) and colleagues reported these findings at the European Committee for Treatment and Research in Multiple Sclerosis meeting in 2007, and now publish them in *Neurology* (early online publication, March 3, 2010). The study was supported by MediciNova, Inc.

Background: Multiple sclerosis occurs when the immune system attacks the brain and spinal cord, damaging nerve fiber-ensheathing myelin and the nerve fibers themselves. Damage to nerve fibers is believed to contribute to the progression of disability in MS. Although there are disease-modifying therapies approved for MS, none directly addresses damage to nerve fibers and the progression of disability. Ibudilast is an oral agent that inhibits an enzyme called phosphodiesterase, resulting in suppression of inflammation. It is marketed in Japan and Korea to treat cerebrovascular disorders and asthma.

The Study: In this study, 271 people with relapsing-remitting MS, and 21 people with secondary-progressive MS experiencing continued relapses were randomly assigned to receive ibudilast at low or high dose (30 or 60 mg) or placebo for 12 months. Participants were then given the option of going on or continuing on active treatment during an open-label phase for another 12 months, and so were followed for a total of 24 months.

The pre-established, primary endpoint was the cumulative number of new or newly enlarged lesions (areas of tissue damage) observed on MRI scans over 12 months. Secondary endpoints

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included time to first relapse, number of relapses, and changes in relapse rates. The team also tracked changes in EDSS (a scale measuring disability) at 12 and 24 months, and brain tissue volume loss, and performed an analysis following the study of MRI abnormalities (called T1 black holes) that indicate nerve fiber loss.

Surprisingly, there was no significant difference seen between the groups in the study's primary endpoint -- the accumulation of disease activity observed on MRI, nor in relapse rates. However, MN-166 was associated with a significant reduction in the loss of brain tissue volume over one year, and a significant reduction in T1 black holes. Over two years, there were fewer patients with disease activity progression on the EDSS.

Gastrointestinal side effects increased with ibudilast dose. The most frequent side effects occurring in all groups were respiratory infections, headache, urinary tract infections, and nausea.

Comment: In an accompanying editorial, Robert Fox, MD (Cleveland Clinic Foundation) comments that further confirmation of these results will require larger studies that measure disease progression as a primary outcome. He also notes that the findings raise important questions about immune system activity in progressive forms of MS, commenting that chronic inflammation may play a role in progressive disease.

On its Web site, Medicinova notes that it is not planning to undertake future clinical development of MN-166 for MS until the company enters into a "strategic collaboration to support further clinical development" of this drug.

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Two New Studies Link Epstein-Barr Virus to Risk of Developing MS

Two new studies are adding to an increasing body of evidence that shows a possible role for Epstein-Barr virus (EBV) in the development of MS. Alberto Ascherio, MD, DrPH (Harvard School of Public Health, Boston) and colleagues showed that an EBV-positive blood test preceded MS diagnosis in a large sample of MS cases identified through U.S. military databases. (*Annals of Neurology*, accepted online January 20, 2010) Manuel Comabella, MD (Hospital Universitari Vall d'Hebron, Barcelona) and an international team of colleagues report that reactions to a specific protein associated with EBV were increased in people with MS compared with siblings who did not have MS (*Multiple Sclerosis* 2010;16[3]:355–358)

Background on EBV and MS: The cause of MS, an unpredictable immune-mediated disease that attacks the central nervous system, is unknown, but the disease is thought to occur when susceptible individuals encounter a triggering factor or factors in their environment. Epstein-Barr virus is a herpesvirus known to cause infectious mononucleosis and other disorders. Most people in the general population have been exposed to the virus. Several previous studies have suggested a possible link between EBV and MS, but other infectious agents have also been linked to MS, leading some researchers to suggest that the way the immune system responds to infections, rather than the infectious agent itself, may lead to the onset of MS.

Harvard Study: Dr. Ascherio and colleagues identified 305 cases of definite or probable MS in the electronic databases of the Physical Disability Agencies of the U.S. Army and U.S. Navy reported between 1992 and 2004, which had at least one blood sample collected prior to the date of MS onset. For each case, they obtained up to three blood samples (the earliest and latest available, as well as a third sample collected between those two). Two controls who did not have MS were chosen from the databases for each case.

At the start of the study, all of the 305 MS cases except for 10 (3.3%) and all of the 610 controls except for 32 (5.2%) had blood samples that tested positive for EBV. A positive

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blood test means that the individual's immune system had at some point been infected by the virus and mounted an immune response against it. All of the 10 initially EBV-negative cases became positive before the onset of MS, but only 10 (35.7%) of the 28 controls became positive. They found no significant association between another virus – cytomegalovirus – and MS risk. The authors conclude that MS risk is low in individuals who have not been infected with EBV, and increases significantly in those individuals following EBV infection.

"This study suggests that conversion to EBV-positive status increases the risk of being diagnosed with MS," said Nicholas LaRocca, PhD, Vice President of Health Care Delivery and Policy for the National MS Society, who served on the planning committee of the Society's 2009 International Workshop On MS Risk Factors And Frequency. Proving a "cause and effect" relationship between EBV and MS requires many research steps. One of these steps is to show that EBV precedes MS, and these authors have shown evidence for that. "Now, we need more studies to confirm this finding. If EBV is to be identified as an MS trigger, we also need to show – and this is the most difficult step – a causal connection." More research in this area is ongoing.

Barcelona Study: If MS is triggered in susceptible individuals by exposure to a virus, then why do siblings brought up in the same household – and presumably exposed to many of the same strains of viruses and infections – differ in terms of their risk for developing MS? Taking one approach to this question, Dr. Comabella and colleagues evaluated the immune system response to various virus-related proteins – including EBV, cytomegalovirus, and measles – evident in blood samples from 25 people with MS, compared with 49 of their siblings who did not have MS.

The investigators found that siblings did not differ in terms of showing signs of having been infected with any of the viruses tested. The only marked difference they found was in the immune responses to EBNA1, a viral protein associated with EBV. These responses (IgG) were significantly increased in people with MS compared with their unaffected siblings. The authors conclude that further studies are needed to understand the mechanism by which immune responses to an EBV protein might contribute to MS.

Read more about the search for the factors that trigger MS.

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Trial of Low-Dose Naltrexone Finds Preliminary Benefit to Mental Health Quality of Life for People with MS

Results from a pilot clinical trial involving 60 people with all types of multiple sclerosis, testing low-dose Naltrexone, a drug approved for treating addiction, suggest that it may improve several measures of mental health quality of life and pain, and that further testing in larger numbers of individuals may be warranted. The study, by Bruce Cree, MD, Douglas Goodin, MD, and colleagues (MS Center, University of California at San Francisco), was presented at the 2008 American Academy of Neurology meeting and has been accepted for publication and now online in the *Annals of Neurology*.
http://www3.interscience.wiley.com/journal/123289912/abstract

Background: Naltrexone is approved by the FDA for the treatment of addictions to opioids and alcohol. At the full recommended dose, Naltrexone blocks opioid docking sites on cells. At significantly lower doses, it has been prescribed as a treatment for a variety of diseases, including various types of cancers, HIV/AIDS, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), emphysema, as well as MS and other autoimmune diseases. Up until now, there has been limited clinical study of low dose Naltrexone (LDN) to treat MS.

Results of a small trial of LDN were presented by Dr. Gianvito Martino (San Raffaele Hospital, Milan, Italy) at the 2008 Academy of Neurology meeting. The team administered 5 mg of LDN to 40 people with primary-progressive MS for 6 months, evaluating its safety and effects on spasticity, pain and fatigue. Five patients dropped out. Significant improvements were shown in fatigue and depression. Transient increases in liver enzymes, urinary tract infections, mild agitation and sleep disturbance were the most common adverse events.

LDN has also been investigated to a limited degree in animal models of MS. The National MS Society funded a pilot study by Ian Zagon, PhD (College of Medicine at Pennsylvania State University) looking at the effects of both low- and high-dose Naltrexone in mice and impacts

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on the MS-like disease, EAE. Based on earlier findings that opioids (which occur naturally on cells in the nervous system) may regulate immunity, wound healing, and cell renewal, Dr. Zagon and colleagues were looking to see if mice treated with Naltrexone demonstrate any changes in their MS-like symptoms or underlying disease activity. His team found that low-dose naltrexone, but not high-dose naltrexone, was somewhat protective against the development of EAE. (Exp Biol Med (Maywood). 2009 Nov;234(11):1383-92. http://www.ncbi.nlm.nih.gov/pubmed/19855075)

This Study: Bruce Cree, MD (University of California, San Francisco) and colleagues conducted a placebo-controlled study in which 80 people with different types of MS were enrolled, but only 60 completed the trial. The trial was supported by private contributions from people with MS and their families. Some participants were using standard disease-modifying therapies during the trial and some were not.

All participants received both the LDN for eight weeks and inactive dummy pills (placebo) for eight weeks in a study design known as "crossover," with one week free of treatment in between. Some received the LDN during the first eight-week period and some during the second eight-week period.

Participants were given a Web-based battery of quality of life tests called the MS Quality of Life Inventory (MSQLI) before the first treatment period and after each study period. The MSQLI asks the individual to report on mental and physical aspects of their condition including mental health, pain, perceived cognitive deficits, fatigue, and visual, bladder and bowel symptoms and sexual satisfaction.

Results: The investigators found that LDN significantly improved quality of life (specifically, mental health, pain, and self-reported cognitive function), but no impact was observed on aspects of physical quality of life (such as fatigue, bowel and bladder control, sexual satisfaction, and visual function). Vivid dreaming was reported during the first week of treatment by some patients, but no other adverse effects were reported. The investigators emphasized that the results did not support the use of LDN instead of proven MS treatments.

The investigators suggest that LDN may provide symptomatic relief for MS. Based on some published laboratory studies, the investigators cite the possibility that LDN increases levels of endorphins in the brain, which are the body's natural pain relievers. Unfortunately, as noted by the investigators, due to dropouts and incomplete data, they had complete data on only 60 of the 80 original participants, which weakened the statistical power of the trial results. They suggested that their findings require confirmation in a larger, multi-center clinical trial.

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