The MS Treatment Landscape:

MSAA's 2014 *MS Research Update* Provides Vital Information to Medical Professionals, Members of the MS Community

New publication compiles the latest developments in MS research.

BY SUSAN COURTNEY AND THE MULTIPLE SCLEROSIS ASSOCIATION OF AMERICA

Recognizing the constant need for information on the very latest developments in MS research, the Multiple Sclerosis Association of America (MSAA) recently published its annual *MS Research Update.* This free 48-page overview of approved disease-modifying therapies, as well as numerous experimental drugs currently under investigation, provides vital facts and recent study findings on each treatment (available online at mymsaa.org/publications/msresearch-update-2014).

Historically, multiple sclerosis (MS) has been a complicated and challenging disease for neurologists to treat. Prior to 1993, when Betaseron® (interferon beta-1b) was approved by the United States Food and Drug Administration (FDA) for the long-term treatment of MS, no disease-modifying therapies were available. In addition to symptomatic treatments, neurologists were limited to prescribing steroids in an attempt to reduce the severity of a relapse. Nothing, however, could be done to slow the disease process or delay debilitating disability.

More than 20 years later, neurologists are now in a much better position for treating this disease. To date, 10 disease-modifying therapies have been approved for the long-term treatment of MS, with more on the way. (Please note that two of these 10 are the same product—Betaseron and Extavia®—but marketed by different companies and managed through different patient programs.) These approved treatments have changed the entire climate of office visits with MS patients, from that of frustration and hopelessness with no treatments to prescribe, to that of enthusiasm and promise for the future—with many treatment options from which to choose.

With so many FDA-approved treatments available, as well as many experimental treatments in the pipeline, staying abreast of the latest developments in research, efficacy, safety, prescribing information, and patient-monitoring programs has become the new challenge for neurologists and patients alike. Neurologists need to evaluate which therapy may be the best choice for each individual patient—in terms of administration, effectiveness, and potential side effects. At the same time, individuals with MS and those close to them want to know which drug will work the best and carry the fewest risks. Many patients are even doing their own research today, frequently asking for opinions from their specialists about various experimental treatments and when they might be available.

In February 2014, to help medical professionals and members of the MS community stay informed of the latest developments in MS research, MSAA released its newest edition of the *MS Research Update.* The information given is based on a wide range of sources, including the extensive, peer-reviewed journal literature on MS and its management, a review of ongoing clinical trials, and

papers presented at major national and international conferences. These include the 2013 conferences hosted by the American Academy of Neurology (AAN), the Consortium of Multiple Sclerosis Centers (CMSC), and the American and European Committees for Treatment and Research in Multiple Sclerosis (ACTRIMS and ECTRIMS).

NOTES FROM THE UPDATE'S AUTHOR AND REVIEWER

MSAA's *MS Research Update* is written by Stephen Krieger, MD, who completed a fellowship at the Corinne Goldsmith Dickinson Center (CGDC) for MS at Mount Sinai. Dr. Krieger has a clinical practice at the CGDC for MS, and participates in several MS clinical trials, including those that study oral therapies and monoclonal antibodies. Dr. Krieger is on many advisory boards in the field of MS, and has presented original work on MS at the AAN, ECTRIMS, ACTRIMS, and CMSC meetings. He is a noted educator and is the neurology residency program director at Mount Sinai.

Dr. Krieger explains, "The expanding arsenal of MS therapeutics has made the decisions facing both neurologists and their MS patients more complex than ever before. MSAA's *MS Research Update* is designed to be a comprehensive and timely resource, not only for neurologists and other MS specialists, but also for patients and their family members, who need to be highly informed about their treatment options. More than ever before, patients now play an active role in the decision-making process when choosing their MS treatment strategy. This publication should facilitate and foster the clinician-patient dialogue that is so important for therapy selection."

MSAA's *MS Research Update* is also reviewed and edited by MSAA's Chief Medical Officer Jack Burks, MD. In addition to his position at MSAA, Dr. Burks is president of Burks & Associates, with an office based in Florida. He is an international MS neurologist, writer, lecturer, and researcher, who assists with the development of new MS therapies and advises patients, families, MS organizations, and healthcare groups. Dr. Burks is a clinical professor of neurology for the Herbert Wertheim College of Medicine at the Florida International University in Miami.

According to Dr. Burks, "Dr. Krieger achieved MSAA's primary goal of unraveling the latest complex scientific MS-research information for patients and other members of the MS community in this understandable publication. At the same time, he accomplished the secondary goal of providing a comprehensive wealth of new MS-treatment data for neurologists and other healthcare professionals. Anyone seeking a concise and thorough overview of approved and experimental disease-modifying therapies for MS will want a copy of this free publication to keep on hand for vital updates and immediate answers to their questions."

TOPICS FEATURED INSIDE THE NEW *MS RESEARCH UPDATE*

A full range of exciting topics in MS research is featured in this edition of the Update. To follow are some excerpts from the introduction, touching on the approved treatments for MS, which are described in detail later in the Update.

"The year 2013 marked the 20th anniversary of the FDA's approval of Betaseron®, the first disease-modifying therapy for MS, and the beginning of the MS-treatment era. This medicine, and other available medications that followed, continue to show effectiveness over the long term. Importantly, these medications have also demonstrated a proven long-term safety track record, which is crucial when considering that people with MS often require treatment for decades.

"Preferably, treatment is now often started when a person is diagnosed as having a clinically isolated syndrome (CIS). This is defined as a single attack (or the appearance of one or more symptoms characteristic of MS), with a very high risk of developing MS, when no other diseases or causes for symptoms are apparent. The use of magnetic resonance imaging (MRI) scans to identify lesions characteristic of MS has taken away the need to watch and wait for a second attack of MS in order to make this diagnosis. Numerous studies with multiple types of disease-modifying therapies (DMTs) have confirmed that early treatment at the time of CIS is beneficial in the long term."

Following the introduction, MSAA's *MS Research Update* lists all of the approved disease-modifying therapies according to their route of administration. These begin with the self-injected medications, continue to those given via intravenous (IV) infusion, and lastly address the newer MS drugs that are given orally. Details on each of these drugs include parent companies, dosages, and types of MS for which these are approved. Modes of action are explained along with recent data from extension studies and post-marketing analyses from periods of up to 20 years following approval. Effects of these drugs on pregnancy, combination studies, labeling changes, and patient safety-monitoring programs are also featured.

In the "Experimental Medications" section that follows the approved therapies, "A New Interferon" gives information about the experimental drug Plegridy™, which is a longer-acting chemical modification of interferon beta-1a. Then the Update addresses experimental medications administered orally (Laquinimod and cladribine). These

TABLE 1. THERAPIES FOR THE MANAGEMENT OF MS
The following therapies are discussed in MSAA's 2014 MS Research Update

FDA-Approved Medications	Experimental Medications
ministered via Self-Injection	*A New Interferon*
Avonex® (interferon beta-1a)	Plegridy™ (PEGylated interferon beta-1a)
Betaseron® (interferon beta-1b)	
Copaxone® (glatiramer acetate)	*Administered Orally*
Extavia® (interferon beta-1b)	Laquinimod
Rebif® (interferon beta-1a)	Cladribine
Administered via Intravenous (IV) Infusion	*Monoclonal Antibody Medications*
Novantrone® (mitoxantrone)	Lemtrada® (alemtuzumab, formerly Campath)
Tysabri® (natalizumab)	Daclizumab (also known as Zenapax®)
	Rituxan® (rituximab)
Administered Orally	Ocrelizumab
Aubagio® (teriflunomide)	
Gilenya® (fingolimod, FTY720)	Ofatumumab (also known as Arzerra®)
Tecfidera™ (dimethyl fumarate, formerly BG-12)	
	Other Therapeutic Strategies
New Directions in MS Research	New S1P Receptor Modulators
	Masitinib (also known as Kinavet® and Masivet®)
Stem Cells	Ibudilast
Neuroprotective Agents	Tcelna™ (formerly Tovaxin®)
Biomarkers	Amiloride
Genetic Studies	Statins
New Therapies Under Investigation	
• Anti-LINGO-1 (BIIB033)	Tetracycline Antibiotics
• Erythropoietin	Vitamin D3
• Idebenone (Catena®, Sovrima®)	Salt
• MIS416	Chronic Cerebrospinal Venous Insufficiency (CCSVI)
• Transdermal Administration of Peptides	
• Secukinumab (AIN457)	
• RTL1000	
• SB-683699 (firategrast)	

are followed by a list of five monoclonal antibody medications (Lemtrada®, daclizumab, Rituxan®, ocrelizumab, and ofatumumab) and several "Other Therapeutic Strategies," such as S1P receptor modulators, Tcelna, Vitamin D3, and reduced salt, to name a few. These are among the many vital areas of interest to MS researchers today. "New Therapies under Investigation" include a number of additional experimental therapies, such as Anti-LINGO, idebenone (similar to coenzyme Q10), and transdermal administration of myelin-related peptides.

In addition to the many therapies described in the Update, the last section provides details on "New Directions in MS Research." Topics include stem cells, neuroprotective agents, biomarkers, and genetic studies – all major areas of study in MS research. For example, biomarkers are a significant research target for many MS investigators. To follow are some excerpts from the information on biomarkers.

"In medicine, the term biomarker refers to anything that can be used as an indicator of a particular disease state; in effect, a biomarker is a surrogate for the disease state. It often refers to a protein measured in blood, whose concentration reflects the severity or presence of disease and/or that can be used to measure therapeutic effectiveness. Many types of biomarkers are being researched in MS, and are likely to grow in importance in the coming years...

"For example, current studies are showing that it may soon be possible to determine who might be a suboptimal

"An additional use of biomarkers will be to predict and minimize the risk of medication-related adverse events. This approach has already proved effective for new infectious biomarkers, such as the development of a blood test for JC virus antibodies, to identify who is at greater or lesser PML risk when treated with Tysabri."

responder to interferons, based on immune system-related substances that can be measured in the blood. Another study was designed to evaluate whether the type of cytokine present prior to treatment with Copaxone might act as a biomarker to identify those individuals with RRMS who are more likely to respond to immunomodulating treatments. It showed that people who responded to Copaxone secreted higher levels of specific inflammatory cytokines prior to treatment. A genetic study, with results reported in 2012, looking at the response to Copaxone, also suggested that multiple genetic markers may predict a favorable response to this medication.

"An additional use of biomarkers will be to predict and minimize the risk of medication-related adverse events. This approach has already proved effective for new infectious biomarkers, such as the development of a blood test for JC virus antibodies, to identify who is at greater or lesser PML risk when treated with Tysabri. Based on this blood test, the option of using Tysabri can be more precisely personalized to maximize the benefit/risk ratio for this medication in practice. This type of biomarker strategy may also prove useful in predicting the risk on an individual basis of non-infectious adverse events to some of the investigational medicines reviewed.

"A strong link exists between biomarkers and genetics, and the line between them may sometimes appear blurred. This is because many of the biomarkers that are being discovered relate to the activity of specific genes that code for proteins involved in inflammation, or are otherwise linked to the response to disease-modifying therapies. Studies of the gene expression signature, through global gene expression analysis, reveals the pattern of the entire DNA in an individual. This type of study has become possible due to recent advances in high-speed genetic pattern analysis." ■

These are just a few samples of the vital and exciting information highlighted in this year's Update. MSAA hopes that many neurologists and other medical professionals take advantage of this important resource. To view or download a free copy of the 2014 MS Research Update, individuals may go to mymsaa.org/publications/msresearch-update-2014. They may also find this publication online by going to MSAA's website at mymsaa.org and then selecting the Publications section (under "About MS"). Printed copies may be ordered at no charge by scrolling to the "Order Publications" option in the Publications section of MSAA's website, or by calling MSAA at (800) 532-7667.

How MSAA Serves the MS Community

The Multiple Sclerosis Association of America (MSAA) is a national nonprofit organization and leading resource for the entire MS community, improving lives today through vital services and support. Founded in 1970, MSAA provides ongoing support and direct services to individuals with MS, their families, and their care partners.

MSAA offers many programs and services to assist individuals with MS. Included among those services are tools to help manage the ever-changing course of multiple sclerosis. These tools are part of MSAA's Shared Management philosophy, involving education, training, use of technology, and tools to promote healthy outcomes. Shared Management is a concept whereby both the patient and healthcare providers work together to achieve the best possible health outcomes for the patient. MSAA's Shared Management tools have been developed to help members of the multiple sclerosis community to be proactive, taking steps toward better health and an improved quality of life. For more information, please visit mymsaa.org/manage-your-ms/sms/.

MSAA's free programs and services include: a Helpline with professional consultants; award-winning publications, including MSAA's magazine, The Motivator; MSAA's nationally recognized website (at www.mymsaa.org), featuring award-winning educational videos and research updates; S.E.A.R.C.H.™ program to assist the MS community with learning about different treatment choices; a mobile phone app, My MS Manager™ (named one of the best multiple sclerosis iPhone & Android apps by Healthline.com); My MS Resource Locator, an MS-specific database with national, state, and where appropriate, local resources, offering information and services; safety and mobility equipment distribution; cooling accessories for heat-sensitive individuals; educational events held across the country; MRI funding; and more. For additional information, please visit mymsaa.org or call (800) 532-7667.