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Update on Deep Brain Stimulation at Mayo Clinic

The goal of deep brain stimulation (DBS) and motor cortex stimulation (MCS) is to restore function or relieve pain by stimulating neural activity through surgically implanted electrodes (Figures 1, 2, and 3). Developed in the 1980s, DBS was principally used to treat movement disorders associated with essential tremor (ET) and Parkinson disease (PD). Today, its applications include other types of movement disorders and certain nonmotor syndromes and conditions. Successful DBS depends on careful patient selection, precise neural targeting, and extensive, individualized programming. It is generally reserved for symptoms that are unresponsive to other therapies.

For 14 years, neurologists, neurosurgeons, and members of the multidisciplinary DBS teams across Mayo Clinic's 3 sites have gained experience, conducted research, and explored new clinical applications. Overall, they agree that for cer-

tain disorders in carefully selected patients, DBS and MCS can markedly improve patient lives. The following update summarizes their findings and experience during the past several years.

Technology Update

The DBS teams at Mayo Clinic in Jacksonville, Florida, and Rochester, Minnesota, are testing the safety and efficacy of a new stimulator that delivers constant current (vs constant voltage) in patients with ET. In theory, the device will automatically sense the need for increased voltage, thus reducing the external programming burden. It can also accommodate more electrodes, thus increasing programming options. Ryan J. Uitti, MD, a neurologist at Mayo Clinic in Jacksonville, points out that several years ago, bilateral electrode placement required 2 stimulators. The new device allows bilateral lead placement served by a single stimulator.

Neurosurgeon Robert E. Wharen Jr, MD, reports that the DBS team in Jacksonville is also exploring the use of intraoperative MRI for tremor. The procedure is conducted while the patient is asleep and eliminates the need for a stereotactic head frame.

Primary Disorders

Essential Tremor

DBS for ET continues to have positive results, and other types of tremor are being addressed. Recently, neurosurgeon Mark K. Lyons, MD, and neurologist Virgilio H. Evidente, MD, his neurology colleague at Mayo Clinic in Phoenix, Arizona, performed the first DBS in the state for orthostatic tremor, a variant of ET that affects the lower limbs on standing and spreads up the trunk. Six months after surgery, the patient shows 60% improvement in both lower limbs with bilateral thalamic DBS. Neurologist Matt Stead, MD, PhD, and neurosurgeon Kendall H. Lee, MD, PhD, at Mayo Clinic in Rochester report success with bilateral



Figure 1. DBS of the targeted group of nerve cells requires implantation of the stimulation electrode, which is secured to the skull and then connected to an infraclavicular neurostimulator (pulse generator).



Ryan J. Uitti, MD

thalamic placement (using 4 leads, 2 on each side) for rubral tremor, a rare tremor associated with the red nucleus, which has been difficult to control with DBS.

Parkinson Disease

In the right patients, DBS continues to be effective in improving motor function and in reducing dyskinesias and symptom fluctuations related to on-off medication effects. The main indication is the patient's need for increased frequency and levels of medication.

Previously reserved for patients under the age of 70 years, DBS is now offered by Mayo physicians to treat older PD patients, some in their 90s. In a retrospective review, Drs Lyons, Evidente, and colleagues found that positive benefit (eg, drug dose reduction) was similar with bilateral placement in the subthalamic nucleus or the globus pallidus interna (GPi). Because the GPi has evidenced fewer cognitive and neuropsychiatric adverse effects, they suggest that it may be a preferred target for PD patients at risk for these sequelae.

Drs Uitti and Wharen and colleagues have found that, in older PD patients with asymmetric motor symptoms, unilateral subthalamic nucleus DBS may be better tolerated relative to short-term confusion, incontinence, and length of hospital stay than bilateral DBS. Drs Lee and Stead note that in some cases, bilateral implantation of 2 leads per side is particularly effective for tremor-dominant PD.

Other Disorders

Dystonia

Patients with focal and generalized dystonia represent a large percentage of Mayo's cases in Rochester. Drs Stead and Lee report good success with DBS for early-onset primary dystonia or early-onset torsion dystonia (DYT1). Most patients with other forms of dystonia are helped,

although the response may not be dramatic. To improve outcomes, the DBS team is considering transcortical magnetic stimulation for some dystonias.

Drs Evidente and Lyons were the first to conduct DBS on a patient with a form of progressive dystonia called *lubag* (its Filipino name), which occurs in 1 of every 4,000 men with maternal roots in the southern Philippines. It is seen in Filipinos worldwide. Five years after surgery, the patient continues to do well, and now other patients with this neurodegenerative disorder are being treated with DBS.

Epilepsy

Mayo Clinic has completed a study of neurostimulation for focal epilepsy. The results are not yet in, but Dr Wharen reports that several patients whose seizures were intractable have become seizure-free. Drs Lee and Stead provided DBS to a 3-year-old patient with Lennox-Gastaut syndrome, the youngest patient to have DBS. The seizures have been markedly reduced and are no longer impeding the patient's development.

Centrally Mediated Neuropathic Pain

Treatment of centrally mediated pain is experimental. The results at Mayo for trigeminal autonomic cephalgia, including cluster headaches, have been mixed. Under consideration is use of preoperative positron emission tomography scans to determine if hypothalamic sites should be stimulated unilaterally or bilaterally in a given patient. Dr Lee says that intractable face pain in the distribution of the trigeminal nerve may respond to MCS. Dr Wharen has used MCS in cases of unsuccessful ablation or gamma knife surgery for trigeminal neuralgia with good results.

Psychiatric Disorders

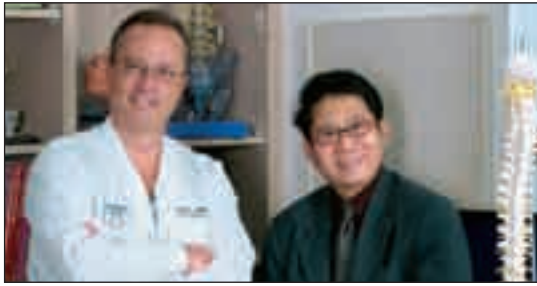
Drs Lee and Stead performed DBS in 2 patients with Tourette syndrome, considered both a



Robert E. Wharen Jr, MD



Figure 2. Final lead placement in motor cortex stimulation for neuropathic pain. Left, conventional implantation of the motor cortex (green gyri); right, more extensive implantation, covering motor, premotor (blue gyri), and some prefrontal cortices. The latter procedure is being performed at Mayo Clinic in Rochester.



Mark K. Lyons, MD, and Virgilio H. Evidente, MD

movement and a psychiatric disorder. They are exploring DBS for other types of tics, and Mayo Clinic is in the early stages investigating neurostimulation for depression and obsessive-compulsive disorder.

Secondary Symptom Benefits

Restless Legs Syndrome

Although DBS has not been used as a primary treatment for restless legs syndrome, Drs Evidente, Lyons, and colleagues noted that there is often a post-DBS reduction in restless legs associated with PD, a finding they confirmed in a retrospective study. Bryan T. Klassen, MD, a DBS fellow at Mayo, has reported a case in which severe periodic limb movements were reduced following DBS for PD. Dr Evidente is now reviewing non-PD cases of ET and dystonia. The tentative results suggest DBS may be a promising option for restless legs syndrome.

Spasmodic Dysphonia

In 2008, Drs Lyons, Evidente, and colleagues presented the first report on improved vocal control in a patient with spasmodic dysphonia who had bilateral thalamic DBS for ET tremor of the hands. Following surgery, there was marked improvement in the patient's spasmodic dysphonia—a primary focal dystonia of the vocal muscles during speech. Dr Lee notes that there are now a growing number of reports of DBS for spasmodic dysphonia outside the United States and that Mayo Clinic may explore this application in the future.

Mechanisms of Neurostimulation

Understanding the mechanisms of DBS and MCS is critical to identifying new targets and making neurostimulation more effective in current applications. Dr Evidente and colleagues are finding indirect evidence of distant effects from DBS. Their study of pre- and post-DBS activity of the Bereitschaftspotential suggests that stimulation of thalamic and subthalamic nuclei has downstream effects on motor cortex.

The Mayo-based multi-institutional DBS Consortium, directed by Dr Lee with Charles Blaha, PhD, at the University of Memphis, Paul

Garris, PhD, at Illinois State University, Pedram Mohseni, PhD, at Case Western Reserve University, and Kevin E. Bennet, chair of Mayo's Division of Engineering, have made great strides in determining the nature of those effects. They recently developed the Wireless Instantaneous Neurotransmitter Concentration Sensing System (WINCS), a device that can monitor neurochemical output of targeted brain sites in real time during DBS. WINCS is providing evidence that modulation of certain central neurotransmitter systems (eg, the entire thalamocortical-basal ganglia circuit) underlies the effects of both DBS and MCS. Continuing their work on the neurochemical basis of DBS, the investigators hope eventually to make the WINCS technology available to monitor neurotransmitter levels in humans during surgery.



Matt Stead, MD, PhD, and Kendall H. Lee, MD, PhD

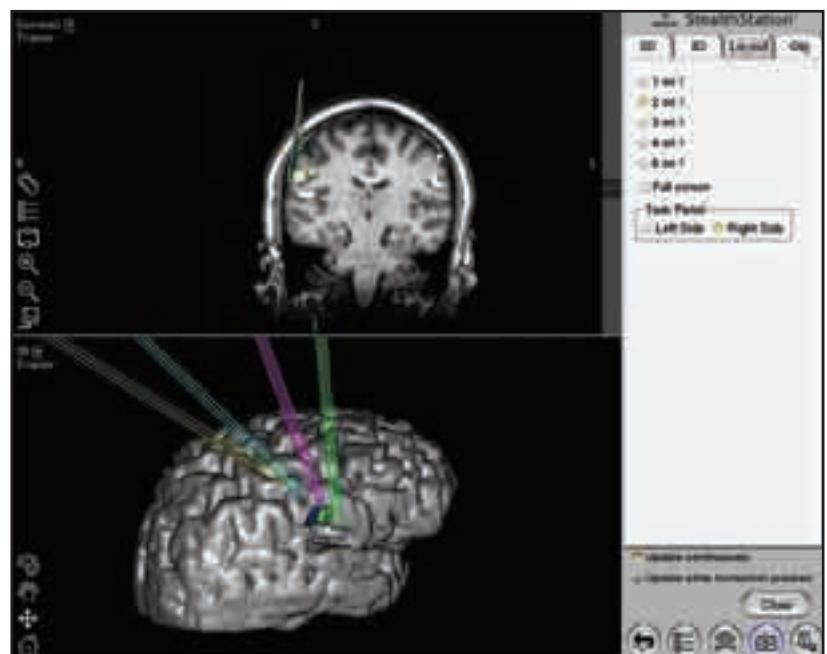


Figure 3. Motor cortex stimulation to treat centrally mediated facial pain. An MRI delineating the location of an electrode with 4 contacts placed across the target—the face area of the motor strip, as defined by a functional MRI scan.

Neuroimaging for Dementia: Current and Future Directions for Mayo Clinic

There is no definitive clinical test to diagnose dementing illnesses. The words “probable” or “possible” are usually attached to their clinical diagnosis. Absolute diagnosis requires tissue examination on biopsy or at autopsy. Yet, as with any disease, early detection is critical to management. Differing forms of dementia—Alzheimer disease (AD), dementia with Lewy bodies (DLB), frontotemporal lobe dementia (FTD), and others—as well as prodromal syndromes of mild cognitive impairment (MCI) must be distinguished from each other and from other neurologic conditions. Knowing the type and severity of the patient’s dementia aids prognosis, family counseling, and therapeutic intervention.

Current medical therapies treat symptoms, but the goal of dementia research is targeted, disease-altering drugs that could halt disease progression. Their development rests on understanding the mechanisms of the various dementias, on accurate diagnosis, and on noninvasive ways of monitoring outcomes in clinical trials. The eventual success of experimental therapies rests on early detection.

Neuroimaging is providing crucial information in all these areas and is benefiting ongoing patient care. Mayo Clinic has long been a world leader in imaging science. Using state-of-the-art equipment, researchers in the Mayo Clinic Imaging Research Center, housed in the new Opus Building on the Rochester, Minnesota, campus, are generating new algorithms and methods of interpreting neuroimages. They work closely with clinical specialists in dementia and with researchers in Mayo’s Alzheimer’s Disease Research Center (ADRC), funded by the National Institutes of Health.

Overview of Imaging for Dementia

Neuroimaging for the dementias includes various magnetic resonance (MR) and nuclear medicine techniques. The glossary in the Table on page 6 summarizes imaging techniques applicable to dementia. As Clifford R. Jack Jr, MD, the radiologist who directs Mayo’s neuroimaging research, notes, “Each imaging technique measures something different about what happens to the brain in the face of pathologic changes associated with a dementing syndrome. Each can provide information about severity, the type of dementia, and specific brain regions involved.”

An image is only as good as its interpretation. Dr Jack, Val Lowe, MD, whose focus is nuclear medicine imaging, and their colleagues are developing new analytic tools or algorithms to refine and transform images into ever more precise and useful information. For example, they are currently updating ways to quantify MRI FLAIR sequencing and to make MR perfusion techniques increasingly applicable to dementia.

New Imaging Applications and Future Directions

Mayo scientists are investigating the latest techniques to identify type and severity of dementia—among them:

Amyloid Imaging: Dr Jack and Ronald C. Petersen, MD, PhD, head of Mayo’s ADRC, agree that amyloid imaging could revolutionize diagnosis and management. Of particular note is its ability to distinguish AD from FTD and its potential use as an outcome measure in clinical trials aimed at reducing amyloid deposition.

Dopamine Active Transporter (DAT): DAT is a SPECT tracer that binds to dopamine receptors in the basal ganglia. It is not yet used in the United States, but is being considered for research studies at Mayo Clinic to identify DLB.

Arterial Spin Labeling (ASL): In MR perfusion studies, ASL is a noninvasive way to measure brain perfusion that is similar to the physiologic information obtained from FDG PET.

Resting State Functional Connectivity: This type of fMRI indirectly measures the degree to which different brain regions are functionally connected but does not require the patient to perform a task. When combined with amyloid imaging, areas active during the resting

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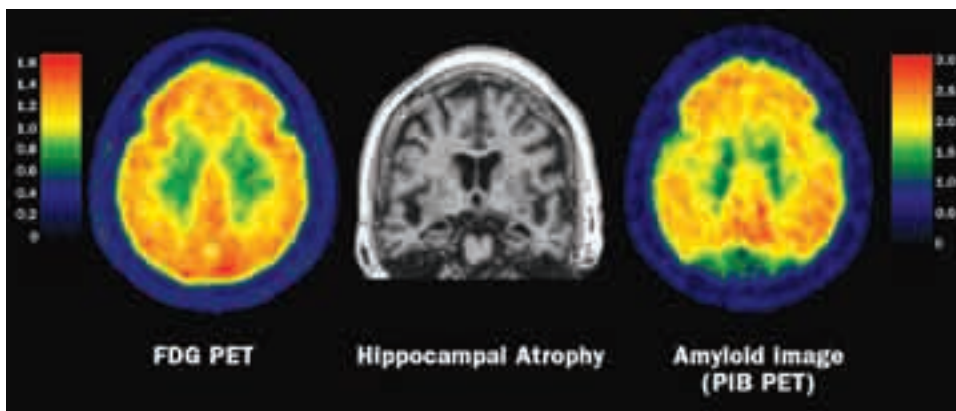


Figure. From left to right: FDG PET, MRI, and PiB PET images of a 79-year-old woman with AD. The color bar for the FDG PET image (on the left) indicates the ratio of cortical uptake to the pons. The color bar for the PiB PET image (on the right) indicates the ratio of cortical uptake to the cerebellum.

Research Highlights

Manipulating Brain Inflammation May Help Clear Brain of Amyloid Plaques

In a surprising reversal of long-standing scientific belief, researchers at the Mayo Clinic campus in Florida have discovered that inflammation in the brain is not the trigger that leads to buildup of amyloid deposits and development of Alzheimer disease. In fact, inflammation helps clear the brain of these noxious amyloid plaques early in the disease development, say the researchers in the *FASEB Journal*. Authors: P. Chakrabarty, K. Jansen-West, A. Beccard, C. Ceballos-Diaz, Y. Levites, C. Verbeeck, A. Zubair, D. Dickson, T. Golde, and P. Das.

Creativity: An Organizational Schema

A Mayo Clinic study published in *Cognitive and Behavioral Neurology* found that despite great qualitative and quantitative differences among people, the human brain functions pretty much the same when it comes to creativity. Researchers found that creativity emerges from motivation, perception, action, temperament, and social context. Author: R. Caselli.

Correlation of Enzyme-Inducing Anticonvulsant Use With Outcome of Patients With Glioblastoma

This Mayo Clinic study of 620 patients found that paradoxically, enzyme-inducing anticonvulsant use correlated with superior outcome of patients with glioblastoma. The study was published in *Neurology*. Authors: K. Jaeckle, K. Ballman, J. Buckner.

Effect of Obesity on Outcome After Temporal Lobe Epilepsy Surgery

Individuals with obesity may have comorbid conditions that increase the risk of general anesthesia and operative procedures. This Mayo Clinic study, published in *Epilepsy Research*, found that perioperative morbidity and seizure outcome following epilepsy surgery was independent of the patient's body weight. However, long-term mortality was significantly increased in individuals with extreme obesity. Authors: C. Kang, G. Cascino.

Survival Profiles of Patients With Frontotemporal Dementia and Motor Neuron Disease

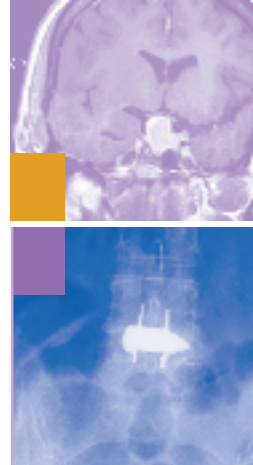
Published in *Archives of Neurology*, this Mayo Clinic study found distinct patterns of survival profiles exist in patients with frontotemporal dementia and motor neuron disease, and overall survival may depend on the relative timing of the emergence of secondary symptoms. Long-term survivors had cognitive onset and delayed emergence of motor symptoms after a long monosymptomatic phase. Authors: W. Hu, H. Seelaar, K. Josephs, D. Knopman, B. Boeve, E. Sorenson, L. McCluskey, L. Elman, H. Schelhaas, J. Parisi, B. Kuesters, V. Lee, J. Trojanowski, R. Petersen, J. van Swieten, M. Grossman.

Anemia or Low Hemoglobin Levels Preceding Parkinson Disease

Results of this Mayo Clinic study support an association between anemia experienced early in life and the later development of Parkinson disease. Published in *Neurology*, the case-control study found anemia was more common in the history of cases than controls, after adjustment for cigarette smoking, exposure to pesticides, or hysterectomy. Authors: R. Savica, B. Grossardt, J. Carlin, M. Icen, J. Bower, J. Ahlskog, D. Maraganore, D. Steensma, W. Rocca.

Failure Rate of Low-Dose Radiosurgical Technique for Vestibular Schwannoma

A Mayo Clinic study of 293 patients with vestibular schwannomas who underwent radiosurgery found that distortion of stereotactic MR imaging coupled with increased radiosurgical conformality and progressive dose reduction likely caused some vestibular schwannomas to receive less than the prescribed radiation dose to the entire tumor volume. This study was published in *Journal of Neurosurgery*. Authors: B. Pollock, M. Link, R. Foote.



To read more about Mayo Clinic neurosciences research and patient care, visit www.mayoclinic.org.

Neuroimaging for Dementia: Current and Future Directions for Mayo Clinic (continued from page 4)



Clifford R. Jack Jr, MD, and Ronald C. Petersen, MD, PhD

state in patients with AD mirror areas that are susceptible to amyloid deposits. Equally important, resting state functional connectivity appears to measure the strength of functional (vs anatomic) connectivity, demonstrating differing patterns of functional loss relative to severity and dementia type.

Future goals for the field include developing a tau protein tracer and one specific to the abnormal protein aggregates associated with DLB and PD.

Clinical Implications

Dr Petersen was the lead investigator in the identification of MCI, a memory disorder considered

a precursor to dementia. It begins with abnormalities in the hippocampus which are visible on structural MRI and critical for early detection. Even now, early detection and differential diagnosis through imaging help determine therapy type. “For example,” Dr Petersen states, “one wouldn’t give a cholinesterase inhibitor that might work in AD to a patient with FTD. Similarly, one wouldn’t give a patient with DLB a dopamine blocker.”

Patients are being actively recruited into ADRC studies. A major goal of imaging research and the ADRC is to identify patterns of disease, work that is being led by Mayo researcher Prashanthi Vemuri, PhD. Many patients with dementia have combined pathologies (eg, a combination of Lewy bodies, vascular disease, and amyloid deposition). Identifying the predominant pathology and lesser ones will permit specifically tailored drug combinations. Advances in neuroimaging are critical to achieving this and other intervention goals.

Table. Glossary of Imaging Techniques for Dementia

Structural MRI: A measure of gross brain anatomy used to detect the presence or absence of atrophy in areas specific to AD, including mesial-temporal lobe structures such as the hippocampus. With disease progression, areas of abnormal atrophy can include the basotemporal lobes, the posterior cingulate, paralimbic cortex, and, eventually, the temporoparietal association areas.

FLAIR (Fluid Attenuation Inversion Recovery): FLAIR imaging helps determine if cognitive changes reflect cerebrovascular disease.

MR Spectroscopy (MRS): This technique measures the concentration of specific metabolites relevant to AD and other dementias, including *N*-acetylaspartate (NAA) and *myo*-inositol. Decrease in NAA is thought to reflect neuron loss in AD. Serial MRS has been used to measure outcomes in clinical trials.

Diffusion-Weighted Imaging (DWI) and Diffusion-Tensor Imaging (DTI): Both techniques measure microscopic diffusion of water molecules in biologic tissue. It is thought that AD disrupts cell membranes, thus increasing the diffusion coefficient of water and decreasing the coherence of directional water diffusion due to loss of neuronal track integrity. Brain maps made from DTI images can illuminate regions of connectivity and loss of connectivity among brain structures.

MR Perfusion: This MRI technique measures regional cerebral perfusion. In AD it shows a bilateral temporal-parietal decrease in blood flow, consistent with perfusion patterns in single-photon emission computed tomography (SPECT) studies and with decreased cerebral glucose metabolism on fluorodeoxyglucose positron emission tomography (FDG PET) studies.

Functional MRI (fMRI): This is an MRI-based measure of cerebral blood flow volume in activated brain regions during functional tasks. Because it requires that the subject perform a directed cognitive task while in the MRI magnet, it is not particularly effective in patients with moderate to severe dementia. However, it has been used to help diagnose MCI and to study patients thought to be at risk. To date, at-risk patients and those with forms of MCI show both increased and decreased activation relative to controls.

Amyloid Imaging: A nuclear medicine-based method of labeling amyloid plaques. The most common binding compound used in Pittsburgh compound B (PiB). Positive PiB uptake occurs in brain regions known to be areas of plaque distribution in AD (eg, frontal lobes, posterior cingulate gyrus, and temporal parietal association cortex).

Aspirin for MS-Related Fatigue

Fatigue is one of the most common and debilitating symptoms of multiple sclerosis (MS). It can affect concentration, muscle strength, and psychosocial well-being. The mechanisms are not understood and may differ among patients. Very few medications are available, and even these may be ineffective for many patients.

B. Mark Keegan, MD, a neurologist and MS specialist at Mayo Clinic in Rochester, Minnesota, says that before prescribing medications, it is important to rule out common factors that may contribute to fatigue in MS patients such as depression, drug therapies, and problems that disturb sleep, including nocturia and sleep apnea. Current medications for MS-related fatigue include amantadine, modafinil, and other stimulants, but as he notes, none of them addresses underlying fatigue mechanisms.

Ten years ago, Dean M. Wingerchuk, MD, a neurologist and MS specialist at Mayo Clinic in Scottsdale, Arizona, and his colleagues noted that some patients taking moderately high doses of aspirin for coexisting conditions such as rheumatoid arthritis reported more energy and less fatigue. They also reported that with reduced doses of aspirin, fatigue worsened.

From this clinical observation, the Mayo team designed a pilot study of 30 patients. Fatigue levels were measured by patient self-report, and results showed aspirin was effective compared with a placebo. To replicate, expand, and further objectify their findings, the team is now conducting a larger study, funded by the National Multiple Sclerosis Society and carried out at all 3 Mayo Clinic sites.

Dr Wingerchuk, principal investigator, explains: "For many years, people have postulated that since MS is an autoimmune disease, inflammation might be a key factor in the

pathogenesis of MS-related fatigue. The well-understood anti-inflammatory mechanisms of aspirin may thus help us understand the relevant mechanisms in MS."

Open Clinical Trial

The goals of the current study are to determine the efficacy and magnitude of the effect of aspirin on MS-related fatigue. A second goal is to more precisely quantify fatigue in order to develop objective measures of therapeutic outcome. In addition to a standard self-report questionnaire, participants will be given cognitive tests of memory and concentration, blood tests to measure inflammation markers, and at the Arizona site, tests of muscle fatigue conducted in a biomechanics laboratory.

To participate, patients must be between 18 and 65 years old, have confirmed relapsing-remitting or secondary progressive MS, be ambulatory for a distance of at least 100 meters without assistance, have had persistent fatigue for 8 weeks not attributable to causes other than MS, and be able to complete cognitive testing and questionnaires. Exclusionary criteria include medical contraindications for aspirin, factors related to other causes of fatigue, and general health problems. Participants who meet enrollment criteria are placed in 1 of 3 groups and given a high dose (1,300 mg/day) or low dose (162 mg/day) of aspirin or a placebo over an 8-week course.

The Mayo research team, which includes Moses Rodriguez, MD, in Rochester and Elizabeth A. Shuster, MD, in Jacksonville, Florida, hopes that in addition to the stated goals, the study will shed light on the role of inflammation in MS-related fatigue.



B. Mark Keegan, MD



Dean M. Wingerchuk, MD

Clinical Trial

Mayo Clinic Clinical Trial on Aspirin for MS-Related Fatigue

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Florida: Pamela Long, RN, 904-953-7719

Minnesota: Darcy Rauchwarter, RN, 507-284-9360

More information, including inclusion and exclusion criteria, is available at

http://clinicaltrials.mayo.edu/clinicaltrialdetails.cfm?trial_id=100795&title=ASA%20for%20MS

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John Noseworthy Elected President and CEO of Mayo Clinic

In November 2009, neurologist John H. Noseworthy, MD, former medical director of the Mayo Clinic Department of Development and, until recently, the vice-chair of the Mayo Clinic Rochester Executive Board, succeeded Denis Cortese, MD, as President and CEO of Mayo Clinic. Dr Noseworthy joined the staff of Mayo Clinic in Rochester, Minnesota, in 1990 and served as chair of the Department of Neurology from 1997 to 2006. He is a professor of neurology in the College of Medicine and a consultant in the Department of Neurology. A clinical specialist in multiple sclerosis with an extensive research record, he trained at Dalhousie University in Halifax, Nova Scotia, and the University of Western Ontario and was a neurology research fellow at Harvard Medical School. Upon election to this new role, he chose to resign as the editor-in-

chief of *Neurology*, the official journal of the American Academy of Neurology. He has written or been the editor of several neurology textbooks, including the 3-volume *Neurological Therapeutics: Principles and Practice*, now in its second edition. Noting that it is a pivotal time in Mayo's history, he states, "Mayo Clinic is all about the patient and delivering the right care to them in the right way. We need to preserve our patient focus while strengthening Mayo Clinic as we address the unique challenges of health care in the 21st century."



John H. Noseworthy, MD

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