The Next Generation of Epilepsy Treatment

Approximately one-third of the 3 million people in the United States with epilepsy continue to have seizures despite taking anti-epileptic medications. Surgery is an option for some but not all of these people. Trials of therapeutic brain stimulation have shown reductions in seizures, but rarely provide seizure-free outcomes. In addition to coping with the side effects of medications and the actual seizure, patients spend much of their lives dreading when the next seizure will strike.

Researchers at Mayo Clinic in Rochester, Minnesota, are at the forefront of developing the next generation of epilepsy treatments. “We’ve embarked over the past decade on building a program of basic science, translational research and clinical trial infrastructure focused on developing new therapies for patients with difficult-to-treat epilepsy,” says Gregory A. Worrell, M.D., Ph.D., a consultant in Neurology at Mayo Clinic in Rochester, Minnesota.

The fruits of that research will be incorporated into the next generation of epilepsy devices that Mayo Clinic is developing in collaboration with Medtronic, the University of Minnesota and the University of Pennsylvania, using a $6.8 million grant from the National Institutes of Health (NIH). The grant — part of the first wave of funding from the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative — is one of only three BRAIN Initiative awards for implantable devices, and the only one of the three directed at epilepsy.

Under the grant’s time frame, implantation of the new device in patients is expected to occur in fall 2018. “We have a clear path to this goal. All the engineering is in place and initial studies are underway,” says Squire (Matt) M. Stead, M.D., Ph.D., a pediatric neurologist at Mayo Clinic with expertise in the use of brain stimulation to treat children with epilepsy and movement disorders.

A fresh look at patients

The path from basic science through clinical trials to new treatments begins with assessing patients’ needs. Mayo Clinic has a large, active clinical practice that offers several options for people with drug-resistant epilepsy.

Two of these options involve devices approved by the Food and Drug Administration (FDA) for treatment of drug-resistant epilepsy.

The first is responsive neurostimulation, in which a pacemaker-like device is implanted in the patient’s skull. The device detects abnormal electrical activity and delivers electrical stimulation to normalize brain activity before the patient experiences a seizure. The second FDA-approved device stimulates the vagus nerve in the neck and has been available for more than a decade.

As described in the June 2015 issue of Neurosurgical Focus, Mayo Clinic has an investigational device exemption from the FDA for an experimental device capable of combined hippocampus and anterior nucleus of the
thalamus stimulation and sensing. Mayo Clinic is also able to offer deep brain stimulation for drug-resistant epilepsy, a treatment approved in many other countries but not in the United States.

Through research and clinical trials, Mayo Clinic has more than a decade of experience using neurostimulation devices. Mayo Clinic is also one of the few centers in the United States utilizing a wide range of these devices—including deep brain, cortical, and hippocampal stimulation—in an effort to individualize brain stimulation.

“When patients come to Mayo Clinic, we look at them freshly and consider the options for those who haven’t responded to medication,” Dr. Worrell says. “Are these patients candidates for epilepsy surgery, or for an approved device? Or would they be better served with one of the experimental protocols that we’re able to do?”

It isn’t uncommon for patients to find treatment options at Mayo Clinic that aren’t available elsewhere. Jamie J. Van Gompel, M.D., a consultant in Neurosurgery at Mayo Clinic, cites the case of a patient who had reflex epilepsy for more than 20 years, causing seizures when he moved his right foot. The patient’s semiology suggested a problem originating in the left motor cortex (Figure 1). After being told that nothing could be done, he came to Mayo Clinic.

“For this type of patient, we consider sub-threshold stimulation,” Dr. Van Gompel says. “Just because the seizure focus is in eloquent tissue, it doesn’t mean we can’t design an implant that may help the patient.”

After evaluating the patient, Dr. Van Gompel implanted a device (Figure 2) that delivers electrical stimulation to the precentral gyrus. The patient’s seizures have eased to the point that, for the first time in years, he is able to put a shoe on his right foot and stand. “We are able to stop a lot of seizures,” Dr. Van Gompel says. “Some patients aren’t seizure-free, but they can certainly see huge improvement.”

Seizure prediction in dogs and humans
Helping patients to become seizure-free is the motivation behind Mayo Clinic’s BRAIN Initiative efforts to develop an improved implantable device for epilepsy. Based on Mayo Clinic’s earlier work, novel devices have already been implanted in patients as well as in dogs with epilepsy. Canine epilepsy is common and often resistant to medication, similar to human epilepsy. The devices being developed and tested provide continuous monitoring of brain activity, and will allow data to be uploaded continuously to the cloud and accessed by researchers.

“We are learning a lot from the dogs,” Dr. Worrell says. “We have good evidence that we can forecast when seizures are going to occur.” Preliminary results of this work were published in the Aug. 4, 2015, issue of PLOS One; further results will be published in Brain.

In addition to seizure prediction, the next generation of devices will provide automated seizure detection, accurate seizure diaries, programmable brain stimulation and treatment algorithms that learn from patients’ brain activity. The ability to stream data from an implanted device to a hand-held device and then via the cloud to the patient’s physician will facilitate communication and treatment.

“The next-generation device will be transformative because we’ll be working with real data,” Dr. Worrell says. “It will provide quantitative information about brain health, just as heart rhythm or blood pressure can be tracked now. We will be able to stimulate the brain based on real information.”

Eventually, Dr. Worrell hopes that devices will help neurologists address common comorbidities of epilepsy, such as mood disorders and problems with memory and sleep.

It might be possible someday to stimulate the brain of an epilepsy patient in ways that ease these problems.

“We imagine a future,” Dr. Worrell says, “where seizures are stopped before they occur, therapies are given at the right place in the right way at the right time, and patients who currently would have had surgeries that might leave them with some functional deficits would be treated with stimulation that can modulate those regions of the brain.”

For more information
Although acoustic neuromas are benign, they can severely affect quality of life. Unilateral hearing loss and tinnitus are common symptoms, and hearing loss can persist after treatment. Observation might be a valid treatment strategy for small, slow-growing acoustic neuromas; however, patients can experience significant anxiety after a tumor diagnosis. When immediate treatment is indicated, physicians and patients must choose between highly specialized options.

Mayo Clinic in Rochester, Minnesota, has strong experience treating acoustic neuroma with a range of treatment options. Treatment is tailored to the needs, both immediate and long term, of the individual patient.

“Acoustic neuroma is a rare disorder that requires very specialized treatment. We have decades of experience and also have done a great deal of research looking at what patients experience after treatment,” says Michael J. Link, M.D., a consultant in Neurosurgery at Mayo Clinic’s campus in Minnesota.

**Individualized treatment decisions**

Acoustic neuromas, which develop in only two to four people per 100,000, are typically discovered on MRI after patients present with unilateral hearing loss, tinnitus, and sometimes dizziness or headache. Surgical removal was once standard treatment; however, reduced tolerance of post-treatment morbidity has resulted in a greater proportion of patients undergoing observation or stereotactic radiosurgery. In a study published in the September 2015 issue of *Otolaryngology — Head and Neck Surgery*, Mayo Clinic researchers found that although the incidence of acoustic neuroma has remained steady over time, tumor size at time of diagnosis has decreased. The researchers also noted a clear, recent evolution in the United States toward managing acoustic neuroma with observation.

“Only about 30 percent of acoustic neuromas show growth four years after diagnosis. In the remaining 70 percent of cases, we can just watch for a while,” Dr. Link says. “But in those cases, patient anxiety must be managed. A major finding of our research is that having a diagnosis of acoustic neuroma significantly impacts a person’s quality of life, even though the tumor is benign and possibly small.” In addition to reassurance, Mayo Clinic patients have follow-up MRI and hearing tests six months after diagnosis, and yearly after that.

Treatment is generally recommended for patients whose tumors are growing or who have symptoms amenable to treatment, particularly if those patients are young. Outcomes are generally good, whether treatment involves stereotactic radiosurgery or surgical removal of the acoustic neuroma (Figure).

“When treated by an experienced team, most patients with small to medium tumors experience high rates of tumor control and excellent facial nerve outcomes, regardless of treatment modality,” Dr. Link says. Indeed, in the largest quality-of-life study conducted among acoustic neuroma patients, published in the April 2015 issue of the *Journal of Neurosurgery*, Mayo Clinic researchers and colleagues in Bergen, Norway, found that patient-related factors such as overall physical and emotional health have a stronger impact on quality of life than treatment strategy does.

Although tumors can be successfully controlled, many patients continue to experience symptoms after treatment. Regardless of treatment strategy, the long-term prospects for hearing in the affected ear are poor. More than 75 percent of patients studied had non-serviceable hearing in the affected ear eight years after treatment for acoustic neuroma, according to a paper by the Mayo Clinic and Bergen researchers published in the August 2015 issue of *Neurosurgery*. Similarly, as described in a study published in the November 2015 issue of the *Journal of Neurosurgery*, long-term severe headache is driven more by patient-related factors than by tumor size or treatment modality. Treatment modality also doesn’t appear to affect long-term dizziness, as described in a Mayo Clinic study in the December 2014 issue of *Otolaryngology — Head and Neck Surgery*.

“We’ve learned that there’s not a big advantage of one treatment over another for long-term quality of life,” Dr. Link says. “But when we spend time talking with a patient, we can usually figure out...
Intraoperative monitoring (IOM) to measure neural function and integrity is an established strategy to reduce the risk of injury occurring during surgery. For maximum effectiveness, IOM requires close cooperation between neurophysiologists and neurosurgeons. At Mayo Clinic, IOM is used extensively in spinal, cranial and brain-stem surgeries, with neurologists and neurosurgeons consulting on pre-surgery planning as well as working together during procedures.

“Our Neurosurgery and Neurology departments are integrated, so surgical procedures are a collaboration between the two services,” says Bernard R. Bendok, M.D., chair of Neurosurgery at Mayo Clinic in Phoenix/Scottsdale, Arizona.

“Intraoperative monitoring is the ultimate team-based practice,” adds Joseph I. Sirven, M.D., chair of Neurology at Mayo Clinic’s campus in Arizona. “IOM is characterized by real-time instant communication between neurologist and neurosurgeon, all with the goal of a positive outcome for the patient.”

At Mayo Clinic, IOM is performed by highly trained technicians and monitored by a neurophysiologist on-site, not at a remote location. Standard protocols help ensure uniform procedures to maintain quality control. “It’s the Swiss cheese model of safety — everyone plays a certain role, and there are checks and balances throughout the process,” says Eric J. Sorenson, M.D., a consultant in Neurology at Mayo Clinic in Rochester, Minnesota.

Awake and playing music
At Mayo Clinic’s campus in Arizona, awake brain surgery is an option for surgical treatment of tumors, focal epilepsy, cavernous malformations and select arteriovenous malformations. “Awake surgery is the ultimate neurological monitoring,” Dr. Bendok says.

Electrical stimulation of the brain is used before surgery to assess the functioning of brain...
tissue. During cranial incision and closing, the patient is under mild intravenous sedation and can respond to requests to perform tasks. Patients with musical ability might be asked to play a musical instrument during surgery.

Awake brain surgery allows surgeons to maximize resection of tumors while minimizing damage to eloquent brain tissue. “Assessment of the functioning of tissue before resection, augmented with awake surgery, provides a strong safety umbrella,” Dr. Bendok says, adding that patients who undergo awake brain surgery for neurovascular disease generally have shorter hospital stays and less discomfort.

The number of awake brain surgeries at Mayo Clinic’s campus in Arizona grew from 20 in 2014 to almost 120 in 2015. A neurologist is present in the operating room during awake brain surgery cases. “That participation is absolutely critical,” Dr. Bendok says. “The neurologist has met the patient beforehand and can follow the neurological exam during surgery based on his or her knowledge of electrophysiology and of the patient’s case. So the entire operation can be tailored to the particular patient.”

Innovation from collaboration
Mayo Clinic has a distinguished history in neurophysiology, particularly in the development of electromyography (EMG). EMG, electroencephalography and evoked potentials (Figure) are used frequently in surgeries of the cervical, thoracic and lumbar spine as well as in brainstem and cranial procedures. Monitoring plans are developed and baseline recordings are taken before surgery, with additional recordings taken during critical parts of the procedure, such as tumor removal or insertion of spinal hardware.

Collaboration between neurosurgeons and neurologists can lead to innovation that increases patient safety. James C. Watson, M.D., a consultant in Neurology at Mayo Clinic’s campus in Minnesota, recalls a Mayo Clinic neurosurgeon expressing interest in IOM of nerves controlling facial muscles near the eyes. Although such a test existed, it didn’t yield consistent recordings. Working with neurosurgeons, Dr. Watson and colleagues developed a more effective technique.

“If we don’t work together, we can’t plan the most efficient way to get the information we need to keep the patient safe,” Dr. Watson says. “As a neurophysiologist, I don’t know what the surgeons see during a procedure or what they need to put in the surgical field. They don’t know what I have the capabilities to monitor. Together, we can meet our shared goals of patient safety and identification of risk in real time.”

Jamie J. Van Gompel, M.D., a consultant in Neurosurgery at Mayo Clinic’s campus in Minnesota, agrees that cooperation between neurologists and neurosurgeons in IOM is increasingly important. “We’re figuring out ways to talk the same language preoperatively, to increase patient safety,” he says.

At Mayo Clinic, on-site neurophysiologists communicate with surgeons and IOM technicians and can enter the operating room if necessary. IOM technicians receive six to 12 months of additional training at Mayo Clinic before they lead monitoring during a procedure.

“Intraoperative monitoring is a niche practice. It takes a lot of skill and commitment to do it well,” Dr. Sorenson says. “At Mayo Clinic, there’s a great deal of trust between the surgeons, anesthesiologists, neurophysiologists and technicians. We all know one another.”

The benefits of IOM are difficult to quantify, as rigorous comparisons of surgical cases pose challenges. However, “every week we see cases where the nerve responses decline during surgery, the team intervenes — maybe pushing blood pressure, or the surgeon taking a step back and reversing something — and then the responses come back up,” Dr. Watson says. “If the responses look good at the end of surgery, then hopefully we’ve preserved some neurological function that was at risk in surgery.”

![Figure](image)

Figure. A. Illustration shows normal motor response in evoked potentials monitoring. B. Minor fluctuations in the motor responses can arise during surgery due to changes in anesthesia. C. Abrupt loss of motor response raises concerns of neurological injury during surgery.
Severe Spinal Deformity Correction

As a major tertiary center for neurosurgery, Mayo Clinic is able to correct even the most severe spinal deformities. Procedures on complex deformities are undertaken in children and adults, and are available at all Mayo Clinic campuses.

Recently, neurosurgeons at Mayo Clinic in Jacksonville, Florida, performed a complex surgical correction of a double major curve in a young woman with scoliosis, with excellent results (Figure). The patient was diagnosed in childhood with scoliosis, which remained stable through adolescence. However, the scoliosis worsened in early adulthood, resulting in an increasingly noticeable hump on her back, pain that interfered with her functioning and quality of life, and shortness of breath. Her condition hindered her ability to work and to care for her young child.

The patient was evaluated by H. Gordon Deen Jr., M.D., and Mark A. Pichelmann, M.D., both consultants in Neurosurgery at Mayo Clinic in Jacksonville, Florida. The surgical team included both of the neurosurgeons as well as a neuroanesthesiologist, an intensive care specialist and nursing staff with experience in complex spinal surgeries.

The surgery was performed in two stages: a fusion of the anterior lumbar spine between L5 and S1, followed a few days later by a posterior decompression and fusion of the spine from T3 to the pelvis, including insertion of rods and screws, and bone grafting.

“We were able to completely straighten the patient’s back, significantly relieve her back pain and help her breathing capacity as well,” Dr. Deen says. “Our patients can have an excellent result, even with very complex surgery, because of our team approach. For a complex problem, it’s important to have a team of experts helping to take care of the patient.”

The procedures for the double major curve correction utilized intraoperative monitoring of the spinal cord to enhance the patient’s safety as well as intraoperative CT image guidance. The enhanced image guidance available at Mayo Clinic facilitates placement of more-robust implants with novel trajectories to better stabilize complex spinal deformities.

“Image guiding also allows us to identify any issues and make modifications during the operation, as opposed to getting a CT two days after surgery and possibly having to return to the operating room to make corrections,” Dr. Deen says.

These technologies, along with improvements in instrumentation and surgical techniques, enable Mayo Clinic neurosurgeons to treat more complex cases than was previously possible. “It is a real pleasure to see a young patient benefit from Mayo Clinic’s expertise — to see how she was able to recover and return to her normal activities,” Dr. Deen says.

Figure. Radiographic images of the woman before and after surgery to correct severe spinal deformity.
Research Highlights in Neurology and Neurosurgery

Contact Sports and CTE
Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disorder linked to repetitive traumatic brain injury and characterized by hyperphosphorylated tau at the depths of sulci. Clinical symptoms usually occur eight to 10 years after exposure to repetitive brain injury. Researchers at Mayo Clinic in Jacksonville, Florida, examined cerebrocortical samples from the Mayo Clinic brain bank, which holds brains of individuals with a range of neurodegenerative disorders as well as neurologically normal controls. Among the 1,721 cases studied, 66 males had a documented history of nonprofessional contact sports during their youth or young adult years. Twenty-one of those former athletes (32 percent) had evidence of cortical tau pathology consistent with CTE. CTE pathology wasn’t detected in 198 individuals without exposure to contact sports, including 33 people with documented single-incident traumatic brain injury sustained from falls, motor vehicle accidents, domestic violence or assaults. There were no significant differences in genetic variants for the cases with CTE pathology. This study is the first to use CTE neuropathologic criteria established by the National Institute of Neurological Disorders and Stroke to look for incidence of disease in nonprofessional athletes. (Bieniek KF, et al. Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. Acta Neuropathologica. 2015;130:877.)

Musical Hallucinations and Neurological Conditions
The phenomenon of musical hallucinations — in which individuals perceive music in the absence of an external auditory stimulus — has been linked to neurological conditions, but hasn’t been fully elucidated. In a case series, researchers at Mayo Clinic in Rochester, Minnesota, found that musical hallucinations can occur in association with a wide variety of conditions, of which neurological disease and brain lesions represent a substantial proportion. The researchers examined the medical records of 393 patients treated at Mayo Clinic from Jan. 1, 1996, to Dec. 31, 2013, who had musical hallucinations. Cases were divided into five categories based on comorbid conditions associated with musical hallucinations: neurological, psychiatric, structural, drug effect and not otherwise classifiable. Variables, including hearing impairment and the presence of visual and other auditory hallucinations, were evaluated independently in all five groups. Neurological disease and focal brain lesions were found in 25 percent and 9 percent of the total cases, respectively. Sixty-five individuals were identified with a neurodegenerative disorder, with Lewy body disorders being the most common. Structural lesions associated with musical hallucinations involved both hemispheres with a preference toward the left, and all but two included the temporal lobe. Hearing impairment was common, particularly in the not otherwise classifiable category; 67.2 percent of individuals in the category had documented hearing impairment. Those with an underlying neurodegenerative disorder or isolated hearing impairment tended to hear more-persistent music, which was often religious or patriotic, compared with those with a structural lesion, where more-modern music was heard, and those with psychiatric disorders, for whom music was mood congruent. The researchers note that a prospective study is needed to further delineate an association between musical hallucinations and neurodegenerative diseases. (Golden EC, et al. Minds on replay: Musical hallucinations and their relationship to neurological disease. Brain. 2015;138:3793.)

Biopsy for Early Detection of Parkinson’s Disease
Finding a peripheral tissue biopsy site to diagnose early Parkinson’s disease (PD) would be of value for clinical care, biomarker validation and research enrollment criteria. Autopsy and advanced PD studies have suggested that the submandibular gland is an important biopsy site; however, early PD hasn’t been studied. Researchers at Mayo Clinic in Phoenix/Scottsdale, Arizona, found that submandibular gland needle biopsy can reveal Lewy-type alpha-synucleinopathy in early PD. Thirty-five study participants underwent transcutaneous needle core biopsies of the submandibular gland. Twenty-five participants had PD of less than five years’ duration; the remaining 10 participants were controls. Tissue was stained for phosphorylated alpha-synuclein and reviewed blind to clinical diagnosis. Only nerve element staining was considered positive. Six patients with PD and one control subject had inadequate glandular tissue. Positive staining was found in 14 of 19 (74 percent) of the remaining patients with PD and two of nine (22 percent) control subjects. Positive and negative cases didn’t differ clinically. Adverse events — mainly swelling and bruising — were common, but minor and transient. The researchers suggest that the false-positives may be true false-positives or may represent prodromal PD. If confirmed in larger studies with eventual autopsy confirmations, the potential value of submandibular gland biopsies for early PD may be to aid in clinical trial inclusion or exclusion and eventually to serve as a gold standard for biomarker studies short of autopsy confirmation. (Adler CH, et al. Peripheral synucleinopathy in early Parkinson’s disease: Submandibular gland needle biopsy findings. Movement Disorders. 2016;31:250.)

To read more about Mayo Clinic neurosciences research and patient care, visit www.MayoClinic.org/medicalprofs.
Expedited Patient Referrals to Mayo Clinic
Departments of Neurology and Neurologic Surgery

While Mayo Clinic welcomes appointment requests for all neurologic and neurosurgical conditions, patients with the following conditions are offered expedited appointments:

1. Cerebral aneurysms
2. Cerebral or spinal arteriovenous malformations
3. Brain, spinal cord or peripheral nerve tumors
4. Epilepsy with indications for surgery
5. Carotid disease

Education 2016-2017 Neurology and Neurologic Surgery Continuing Medical Education Programs

2016 courses

June
Neurology in Clinical Practice 2016
June 30-July 3, 2016
The Fairmont Orchid, Kohala Coast, Hawaii

August
Microvascular Surgery Skills Training
Aug. 8-12, 2016
Mayo Clinic, Rochester, Minn.

September-October
Stroke and Cerebrovascular Disease Review — General Session
Sept. 29-Oct. 1, 2016
The Ritz-Carlton, Amelia Island, Fla.

APBN MOC: Stroke and Cerebrovascular Disease Review
Sept. 29-Oct. 1, 2016
The Ritz-Carlton, Amelia Island, Fla.

Stroke and Cerebrovascular Disease Review — Nursing Session Saturday Only
Oct. 1, 2016
The Ritz-Carlton, Amelia Island, Fla.

Transcranial Doppler Hands-on Workshop
Oct. 1, 2016
The Ritz-Carlton, Amelia Island, Fla.

December
Oriented Neuro-Ophthalmology 2016
Dec. 8-10, 2016
The Venetian
Las Vegas

2017 courses

January
Mayo Clinic Radiation Oncology: Current Practice and Future Direction 2017
Jan. 9-13, 2017
The Fairmont Kea Lani
Maui, Hawaii

March
Healing & Re-engineering Minds & Bodies: Ethical Challenges in Neurology, Disabilities and Technology Assessment 2017
March 29-31, 2017
Mayo Clinic
Rochester, Minn.

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