Minimally Invasive Options for Medically Refractory Epilepsy

All three Mayo Clinic campuses offer new, minimally invasive options for the diagnosis and treatment of medically refractory epilepsy. Stereoelectroencephalography (stereo EEG) and laser ablation of tissue are used to localize and treat seizure activity deep in the brain, allowing patients to avoid open surgery.

“Patients with medically refractory epilepsy can benefit hugely from surgery. But the invasive nature of a craniotomy to localize or treat seizures can make patients reluctant to take that step. Stereo EEG and laser ablation change that perception,” says Richard S. Zimmerman, M.D., a neurosurgeon at Mayo Clinic in Phoenix/Scottsdale, Arizona.

For patients with medically refractory temporal lobe epilepsy, Mayo Clinic in Rochester, Minnesota, is enrolling participants in the Stereoelectroencephalography (stereo EEG) and Laser Ablation for Temporal Lobe Epilepsy (SLATE) clinical trial. Mayo Clinic’s campus in Arizona will soon join the trial. SLATE is testing the efficacy of MRI-guided laser ablation for mesial temporal sclerosis that allows patients to avoid open temporal lobectomy.

“Rather than removing tissue so it will not cause seizures, we can heat the tissue, simply by inserting a laser catheter. Through advanced imaging we can see in real time exactly what tissue we’re treating, so we are very accurate,” says Jamie J. Van Gompel, M.D., a neurosurgeon at Mayo Clinic in Rochester, Minnesota, and the trial’s principal investigator at that site.

Successful application of these sophisticated techniques requires close collaboration between neurologists and neurosurgeons. At Mayo Clinic, neurological and neurosurgical services are completely integrated.

“Stereo EEG and laser ablation are truly expressions of what we can do when neurology and neurosurgery work together as a neuroscience team,” says William Tatum, D.O., a neurologist at Mayo Clinic in Jacksonville, Florida. “These procedures can give patients a second look at life. Without it they are neurologically disabled — they often can’t drive, can’t make a living, can’t form interpersonal relationships and have a poor quality of life.”

**Stereo EEG**
Stereo EEG (Figure 1) involves drilling several very small access holes measuring about 2.3 millimeters in diameter in the skull. Under computer-guided
navigation, electrodes can then be placed deep in the brain (Figure 2) to map seizure activity and nearby important and functional tissue.

“Stereo EEG allows us to record from areas in the brain that previously were very difficult to access with electrodes,” says Amy Z. Crepeau, M.D., a neurologist at Mayo Clinic’s campus in Arizona. “When noninvasive testing isn’t enough to zero in on the seizure onset zone, stereo EEG allows us to record from a wider area in the brain. Patients tolerate this method much better than craniotomy and recover more quickly.”

The electrodes are placed under general anesthesia. Patients sometimes spend several days in the epilepsy monitoring unit before returning to the operating room for removal of the electrodes. The neurosurgeon might remove the seizure onset zone at that time or wait a few weeks if the patient needs additional time to recover from the monitoring.

“With stereo EEG, we’re seeing epilepsies in all sorts of locations — the insular cortex, the cingulate cortex — that we never saw before,” Dr. Van Gompel says. “Stereo EEG is system mapping that can probe various areas of the brain that communicate with one another even though they’re not adjacent.”

Once seizure activity is localized, laser ablation can sometimes be used to treat epileptic tissue. “We’re able to combine the minimally invasive diagnostic procedure with a minimally invasive therapeutic approach, sometimes in the same hospitalization,” Dr. Zimmerman says. “Obviously, that depends on the amount of tissue that’s causing the seizures and its location. If it’s a large area of the brain, the patient may need an open surgery. If the site is in an eloquent area, we might implant a neurostimulation device.”

Enrolling patients in SLATE
SLATE is a phase 1, multicenter clinical trial. The MRI-guided system has approval from the Food and Drug Administration for ablation of brain tissue but isn’t indicated for epilepsy treatment. In the trial, about 150 adults between the ages of 18 and 70 will have MRI-guided laser ablation of the amygdala and hippocampus. Over 12 months, study participants will be evaluated for freedom from seizures, quality of life, adverse events and neuropsychological outcomes.

“The big advantage is patient recovery,” Dr. Van Gompel says. “With laser ablation, the patient generally stays in the hospital just overnight and can return to normal activities in a week or so. Open temporal lobectomy means a three-day hospitalization and six to 12 weeks for recovery.

“We tell our patients that we have a higher chance of curing them with the open surgery, but the less invasive laser procedure has a good chance of working,” he adds. “If it doesn’t, we can still do the open procedure that carries an increased risk.”

QT grid for localizing seizures
In addition to stereo EEG, neurologists and neurosurgeons at Mayo Clinic’s Florida campus use a unique intraoperative brain mapping tool, often with the patient awake. The device, known as a QT grid, is a 4-centimeter ring with 22 sensors around the perimeter. It was developed by Dr. Tatum and Alfredo Quinones-Hinojosa, M.D., chair of Neurosurgery at Mayo Clinic’s Florida campus.

The circular grid can surround small areas of the brain, to precisely identify seizure location. Keeping patients awake allows for dynamic testing during the procedure to avoid damage to eloquent tissue.

“We have had extraordinarily positive results in our ability to resect parts of the brain that appear
Groundbreaking Trial of Stem Cell Treatment for ICH

Mayo Clinic is conducting the first clinical trial in the United States of stem cell treatment for intracerebral hemorrhage (ICH). The investigators hope that results of the phase 1 trial, conducted in conjunction with Mayo Clinic’s Center for Regenerative Medicine, will lead eventually to therapies that provide neuronal protection or recovery for people with ICH.

“This is cutting-edge research, using cells as drugs to help to repair the damage that occurs in hemorrhagic stroke,” says Abba C. Zubair, M.D., Ph.D., a consultant in Pathology at Mayo Clinic in Jacksonville, Florida, and a co-principal investigator of the trial. “We haven’t had treatment options that address neuronal recovery or protection of neurons. A regenerative therapy would be highly beneficial.”

Roughly half of hemorrhagic strokes result in death within 30 days. Current treatment modalities focus on controlling inflammation and providing supportive therapies (Figure 1).

“Although significant advances have occurred in the treatment of stroke, the subset of patients with hemorrhagic stroke haven’t benefited as much. We are passionate about raising the level of treatment for ICH closer to our ability to treat patients with ischemic stroke,” says William D. Freeman, M.D., a consultant in Neurology at Mayo Clinic’s Florida campus.

The stem cell clinical trial targets acute ICH treated within 72 hours of stroke onset. “Our preclinical experiments showed that the effects of treatment aren’t as prominent after delay,” says Zubair. “In this clinical trial, we want to target the population that would be most likely to benefit. But in the future, we would hope to study treatment that occurs later.”

Participants in the 12-patient trial will be divided into four groups of three patients. Three of the groups will receive allogenic mesenchymal stem cells intravenously, at three different dose levels. The fourth group, composed of patients who require a brain catheter to reduce pressure from hydrocephalus, will have intraventricular delivery of stem cells through a catheter. “In addition to optimal dosage, we want to study the best method of delivery,” Freeman says.

Possible mechanism of action

In preclinical experiments, Mayo Clinic researchers demonstrated that mesenchymal stem cells (Figure 2) have anti-inflammatory properties and the capacity to rescue injured neurons. In these experiments, neuronal cells were subjected to oxygen-glucose deprivation stress, which resulted in a significant decrease in cell proliferation and an increasing rate of apoptosis, as well as elevated levels of tumor necrosis factor-alpha.

Figure 1. On the left, the CT image shows an intracerebral hemorrhage (ICH) with external ventricular drain (EVD) in the coronal plane. On the right, the drawing illustrates placement of an EVD in an ICH.

Figure 2. Mesenchymal stem cells are fibroblast-like and can adhere to plastics in standard culture conditions.
Mayo Clinic is enrolling patients in a phase 1 clinical trial of adipose stem cell treatment for spinal cord injury caused by trauma. The researchers already have approval from the Food and Drug Administration for subsequent phase 2A and 2B randomized control crossover trials.

Participants in the phase 1 clinical trial must have experienced a trauma-related spinal cord injury (Figure) from two weeks to one year prior to enrollment. They will receive intrathecal injections of adipose-derived mesenchymal stem cells. No surgery or implantable medical device is required.

“That is the most encouraging part of this study,” says Mohamad Bydon, M.D., a consultant in Neurosurgery specializing in spinal surgery at Mayo Clinic in Rochester, Minnesota, and the study’s director. “Intrathecal injection is a well-tolerated and common procedure. Stem cells can be delivered with an implantable device, but that would require surgery for implantation and additional surgeries to maintain the device. If intrathecal treatment is successful, it could impact patients’ lives without having them undergo additional surgery or maintain permanently implantable devices for the rest of their lives.”

To qualify for the trial, patients must have a spinal cord injury of grade A or B on the American Spinal Injury Association (ASIA) Impairment Scale. After evaluation at Mayo Clinic, eligible patients who enroll will have adipose tissue extracted from their abdomens or thighs. The tissue will be processed in the Human Cellular Therapies Laboratories, which are co-directed by Allan B. Dietz, Ph.D., to isolate and expand stem cells.

Four to six weeks after the tissue extraction, patients will return to Mayo Clinic for intrathecal injection of the stem cells. The trial participants will then be evaluated periodically for 96 weeks.

Mayo Clinic has already demonstrated the safety of intrathecal autologous adipose-derived stem cells for neurodegenerative disease. In a previous phase 1 clinical trial, with results published in the Nov. 22, 2016, issue of Neurology, Mayo Clinic researchers found that therapy was safe for people with amyotrophic lateral sclerosis (ALS). The therapy, developed in the Regenerative Neurobiology Laboratory under Mohamad Bydon, M.D.
the direction of Anthony J. Windebank, M.D., is moving into phase 2 clinical trials.

Dr. Windebank is also involved in the new clinical trial for people with traumatic spinal cord injuries. “We have demonstrated that stem cell therapy is safe in people with ALS. That allows us to study this novel therapy in a different population of patients,” he says. “Spinal cord injury is devastating, and it generally affects people in their 20s or 30s. We hope eventually that this novel therapy will reduce inflammation and also promote some regeneration of nerve fibers in the spinal cord to improve function.”

Mayo Clinic’s extensive experience with stem cell research provides important guidance for the new trial. “We know from prior studies that stem cell treatment can be effective in aiding with regeneration after spinal cord injury, but many questions remain unanswered,” Dr. Bydon says. “Timing of treatment, frequency of treatment, mode of delivery, and number and type of stem cells are all open questions. Our hope is that this study can help answer some of these questions.”

In addition to experience, Mayo Clinic brings to this clinical trial the strength of its multidisciplinary focus. The principal investigator, Wenchun Qu, M.D., M.S., Ph.D., is a consultant in Physical Medicine and Rehabilitation at Mayo Clinic’s Minnesota campus, as is another of the trial’s investigators, Ronald Reeves, M.D. Dr. Dietz, the study’s sponsor, is a transfusion medicine specialist. Also involved is Nicolas N. Madigan, M.B., B.Ch., BAO, Ph.D., a consultant in Neurology at Mayo Clinic’s Minnesota campus.

The study team is in discussions with U.S. military medical centers to enroll patients, and discussing additional collaboration with international sites, potentially in Israel or Europe, for future phases of the study.

“At Mayo Clinic, we have a high-volume, patient-centered multidisciplinary practice,” Dr. Bydon says. “That allows us to do the most rigorous scientific trial that is in the best interests of our patients.”

For more information

### Advances in Endoscopic Skull Base Surgery

Mayo Clinic is integrating several sophisticated techniques to provide an advanced approach to endoscopic skull base surgery. These innovations, available at all three Mayo Clinic campuses, enhance the precision of complex skull base surgeries.

“We are bringing together many high-end pieces to provide integrative techniques that don’t happen in a lot of other places,” says Bernard R. Bendok, M.D., chair of Neurosurgery at Mayo Clinic in Phoenix/Scottsdale, Arizona. “It’s an intense area of focus for us, and we are getting referrals from around the world.”

These innovations, used in surgeries to treat pituitary tumors, meningiomas and clival tumors, include:

- Image guidance and intraoperative CT
- 3-D endoscopy
- Simulations that integrate endoscopic surgery and proton beam therapy
- 3-D models (Figure 1, see page 6) and holography (Figure 2, see page 6) for presurgical planning

Mayo Clinic’s integrated, multidisciplinary practice means that an ENT surgeon works alongside the neurosurgeon throughout treatment. “That’s one of our biggest advantages,” says Devyani Lal, M.D., a consultant in Otorhinolaryngology specializing in rhinology-skull base surgery at Mayo Clinic’s campus in Arizona. “Skull base pathology requires combined ENT and neurological expertise. Our integrated approach maximizes our ability to remove tumors completely.”

### High-end technology in many hands

Intraoperative CT provides enhanced visualization to maximize tumor resection. “We’re able to resect a lot of the tumor with less risk to the cranial nerves. We also get a better view of the cavernous sinus, so we can work more safely,” Dr. Bendok says. “Craniotomy is avoided, and we’re able to remove skull base tumors less invasively.”

Angled endoscopes further enhance visualization and surgical precision. “We can look around corners and find a tumor even if it’s hidden behind the carotid artery or in the sphenoidal sinus or up high in the skull base,” Dr. Lal says. “The collaboration between ENT and neurosurgery is a very dynamic process. I work with an endoscope every day of my professional life. During skull base surgeries, I often suggest...”
looking for tumor in certain places. Four hands are better than two, and two brains are better than one.”

Endoscopic techniques are further enhanced via computer simulations that map how that surgical approach can be integrated with proton beam treatment. “That is a fabulous hybrid therapy for chordomas,” Dr. Bendok says. “We use computer simulation to get a volumetric rendering of the tumor. Then, depending on how much tumor we remove, we can determine the dose of radiation that’s needed. Simulations allow us to do the surgery before the surgery.”

The latest innovation in pre-surgical planning involves augmented reality and holography. “We’re incorporating the patient’s anatomy into holography to create holograms of pituitary tumors,” Dr. Bendok says. “We can walk through the patient’s anatomy before surgery.”

**Lower risk, higher function**

At Mayo Clinic, neurosurgeons and ENT surgeons meet weekly to discuss skull base cases. “Because of this combined effort, a multidisciplinary plan is fashioned that is individualized to the patient,” Dr. Bendok says. “We use nasoseptal flaps and other ancillary flaps for skull base repair, resulting in negligible rates of postoperative cerebral spinal fluid leak. We’ve also been doing preoperative embolization and preoperative balloon test occlusion, when necessary, to reduce the risk of stroke from surgery.”

After skull base surgery, Mayo Clinic patients have specialized neurointensive care.

In addition to minimizing risk, Mayo Clinic strives to enhance patient recovery and quality of life. “We don’t do packing of the nose routinely after skull base surgery. As a result, patients are much more comfortable,” Dr. Lal says. “We also focus on functional outcomes. For many of our patients, we are able to restore vision and preserve olfactory function. For secretory pituitary tumors, we shoot for endocrinological cure.

“Our reconstructive surgeons are also involved in resection of large sinonasal and skull base malignancies with intracranial extension, such that needed cancer resection is never compromised,” she adds. “This has helped with our local control and survival rates. No matter how large the resection, our reconstructive surgeons are able to fashion regional and free flaps to repair the defect for pleasing cosmetic and functional outcomes.”

Mayo Clinic’s approach can provide successful care even for people with complex disease. Dr. Lal cites a patient who came to Mayo Clinic’s campus in Arizona with a meningioma pressing on her optic nerve.

“The tumor was in a very difficult location and causing visual compromise,” Dr. Lal says. Reluctant to use radiation near the optic nerve, Dr. Lal and Dr. Bendok opted for surgical resection, approaching the tumor toward the midline.

“We had to be certain that the central retinal artery wasn’t injured during tumor resection,” Dr. Lal says. “Our neuroradiologist mapped out where the artery was, and then we did the surgery. We got all the tumor out, and she left the hospital the next day, with no nasal packing. The patient’s visual loss and field deficit were restored on testing by our ophthalmologists. And although we worked through her nose for about eight hours, she smells and breathes beautifully.”

“Providing this level of high expertise requires strong collaboration, not just with our neurosurgeons and ENT surgeons but also with our neurologists, neuroradiologists, endocrinologists and ophthalmologists,” Dr. Bendok adds. “We bring that expertise to every one of our patients.”

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**Figure 1.** Matthew Welz, a research technologist at Mayo Clinic in Phoenix/Scottsdale, Arizona, demonstrates 3-D printed anatomy that is used to practice surgical removal of skull base tumors.

**Figure 2.** Mr. Welz walks through a holographic version of a brain, complete with arteries and tumor, to allow for visualization of the space before surgery.
Determining the Prevalence of AD Imaging Biomarkers
To identify the effects of interventions for dementia, it’s necessary to understand the prevalence of Alzheimer’s disease (AD) biomarkers in the population without dementia. Researchers at Mayo Clinic in Rochester, Minnesota, have compiled estimates that demonstrate an increasing prevalence of elevated brain amyloid and decreased cortical thickness as markers for neural degeneration among people without dementia. Participants in the Mayo Clinic Study of Aging underwent positron emission tomography (PET) scan to assess brain amyloid accumulation and MRI to assess a composite AD signature cortical thickness measure. The participants were characterized as having elevated amyloid, reduced cortical thickness, both, or neither. Among 1,646 participants without dementia (mean age 70.8 years), the prevalence of amyloidosis was 21.1 percent (24.3 percent among women and 17.5 percent among men). The prevalence of reduced cortical thickness was 28.9 percent (27.9 percent among women and 30.2 percent among men). Although the prevalence of amyloidosis and reduced cortical thickness both increased with age, the prevalence of reduced cortical thickness rose more steeply than amyloidosis after age 69. After age 79, amyloidosis plateaued in men but continued to increase in women. In men and women combined, the prevalence of the biomarker categories for participants ages 50 to 89 were: neither amyloidosis nor reduced cortical thickness, 61.4 percent; reduced cortical thickness alone, 17.4 percent; both amyloidosis and reduced cortical thickness, 11.5 percent; and amyloidosis alone, 9.7 percent. The researchers note that these prevalence estimates are important for understanding age-related trends in amyloid positivity and AD signature cortical thickness in the population, and for potentially projecting the future burden of biomarkers in older adults. (Roberts RO, et al. Weighting and standardization of frequencies to determine prevalence of AD imaging biomarkers. Neurology. 2017;89:2039.)

Cerebrovascular Disease and Marfan Syndrome
Small studies have suggested that Marfan syndrome is associated with a wide range of cerebrovascular complications. In a large case-control study, researchers at Mayo Clinic in Rochester, Minnesota, found that hospitalized patients with Marfan syndrome had only a modestly increased prevalence of ischemic stroke, hemorrhagic stroke and cerebral aneurysms compared with controls. The study used the 2000-2012 National (Nationwide) Inpatient Sample to match more than 13,000 patients who had a diagnosis of Marfan syndrome to controls without that diagnosis. Patients with Marfan syndrome were significantly more likely to have carotid dissection; however, the researchers note that most of the dissections were likely asymptomatic or incidental, as the stroke rate for patients with Marfan syndrome was only modestly higher than the stroke rate for controls. The researchers suggest that modestly heightened risk of cerebrovascular disease might not justify special measures to monitor patients with Marfan syndrome for cerebrovascular disease prevention. However, prospective studies are needed to identify appropriate screening and treatment algorithms. (Kim ST, et al. Increased prevalence of cerebrovascular disease in hospitalized patients with Marfan syndrome. Journal of Stroke and Cerebrovascular Diseases. 2018;27:296.)

Improved Diagnosis of PD Through Detailed Olfactory Testing
Olfactory decline is a hallmark of both normal aging and neurodegenerative diseases, including Parkinson’s disease (PD). Olfactory dysfunction might precede the onset of motor symptoms of PD by up to seven years. Since early clinical diagnosis of PD by standard neurological examination is unreliable, clinical diagnosis might be improved by making better use of olfactory information. Previous studies have reported that a poor overall score on the University of Pennsylvania Smell Identification Test (UPSIT) is correlated with PD, but it hasn’t been clear that the test has sufficient predictive power to be of clinical value. Researchers at Mayo Clinic in Phoenix/Scottsdale, Arizona, and colleagues have found that a more accurate clinical diagnosis can be made using the pattern of responses to all the test questions rather than just the overall test score. The researchers analyzed a large data set from the Arizona Study of Aging and Neurodegenerative Disorders, a longitudinal clinicopathological study of health and disease in elderly volunteers. Using the complete pattern of responses to all 40 items in each individual’s test, the researchers built a predictive model that was subsequently validated out of sample by comparing model predictions against postmortem pathological diagnosis. The researchers also identified specific test questions that carry the greatest predictive power for disease diagnosis. The researchers strongly recommend that clinicians and researchers who administer UPSIT retain specific responses for each of the test questions for each individual taking the test. That more-refined data will enable future investigations of the diagnostic power of olfactory testing. (Gerkin RC, et al. Improved diagnosis of Parkinson’s disease from a detailed olfactory phenotype. Annals of Clinical and Translational Neurology. 2017;4:714.)

To read more about Mayo Clinic neurosciences research and patient care, visit http://www.mayoclinic.org /medical-professionals.
Expedited Patient Referrals to Mayo Clinic
Departments of Neurology and Neurologic Surgery

Education 2018-2019 Neurology and Neurologic Surgery Continuing Medical Education Programs

2018 courses

February
Practical Neuroradiology: Excellence Through Evidence and Guidelines 2018
Feb. 11-15, 2018
Montage Deer Valley, Park City, Utah

March
Caring for the Dying and All Things Hospice Workshop
March 4, 2018
The Fairmont Orchid, Kohala Coast, Hawaii

Hands-On Injection Workshop
March 4, 2018
The Fairmont Orchid, Kohala Coast, Hawaii

Addiction Medicine for Primary Care Providers
March 4, 2018
The Fairmont Orchid, Kohala Coast, Hawaii

Principles of Pain Management and Palliative Care: Essential Tools for the Clinician 2018
March 5-9, 2018
The Fairmont Orchid, Kohala Coast, Hawaii

Mayo Clinic Neurosurgery Updates Symposium 2018
March 8-10, 2018
Ponte Vedra Inn and Club, Ponte Vedra Beach, Fla.

Mayo Clinic Cerebrovascular Update & Controversies: Neurology & Neurosurgery 2018
March 23-24, 2018
Four Seasons, Las Vegas

May
4th Annual Neuro and Intensive Care: Review and Hands-on Workshops 2018
May 10-12, 2018
Loews Portofino Bay Hotel, Orlando, Fla.

June
Microsurgical & Endoscopic Approaches to Aneurysms and Skull Base Disease
June 13-16, 2018
Mayo Clinic Simulation Center, Jacksonville, Fla.

July
Neurology in Clinical Practice 2018
July 19-21, 2018
Westin Chicago River North, Chicago

October
Mayo Clinic Neuroscience and Oncology Innovation Summit
Oct. 18-20, 2018
The Ritz-Carlton, South Beach, Miami

November
Mayo Clinic Convergence Neuroscience 2018
Nov. 8-10, 2018
St. Thomas, Virgin Islands

Microsurgical & Endoscopic Approaches to Aneurysms and Skull Base Diseases
Nov. 14-17, 2018
Mayo Clinic Simulation Center, Jacksonville, Fla.

Mayo Clinic Multidisciplinary Spine Care Conference 2018
Nov. 16-17, 2018

2019 courses

January
2019 Mayo Clinic Spine Course: Surgical & Medical Management of the Aging Spine
Jan. 13-17, 2019
The Fairmont Orchid, Kohala Coast, Hawaii

June
8th Quadrennial International Conference on Vestibular Schwannoma and Other CPA Tumors: Advancing Care through Ideas and Innovation 2019
June 18-21, 2019
Mayo Civic Center, Rochester, Minn.

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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

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