Multiple treatment options available to patients with epilepsy

Some two-dozen antiseizure drugs are now on the market to treat epilepsy, but it is estimated that one-third of the more than 3 million adults in the United States with the disorder continue to experience seizures despite being on medication. This is called medication-resistant epilepsy. “Too often, a level of complacency sets in among doctors and their patients, and they become accustomed to incomplete seizure control,” says John Stern, MD, codirector of the UCLA Seizure Disorder Center. “This is less than optimal, but they are reluctant to go beyond that.”

Living with even occasional seizures has
Patients with dementia benefit from treatment in specialized setting

With improvements in recent years in the ability of specialized centers to diagnose Alzheimer’s disease and other dementias, it has become increasingly clear that many patients who are seen in nonspecialized settings are misdiagnosed. “Memory loss in older adults is often considered to be Alzheimer’s disease until proven otherwise,” says Keith Vossel, MD, MSc, director of the Mary S. Easton Center for Alzheimer’s Disease Research at UCLA. “But as we collect more data, we’re learning that when physicians think a patient has Alzheimer’s disease, the imaging biomarkers suggest they are wrong about one-third of the time.”

The UCLA-Easton Center has a three-pronged mission: to improve the quality of life for patients and caregivers of individuals with Alzheimer’s disease and related conditions, to support research to better understand these conditions and to develop new medications and treatments. “We aim to be a community resource for patients with memory loss and their physicians by providing the best-possible diagnostic workup to ensure accurate diagnosis and appropriate state-of-the-art care,” says Aaron McMurtray, MD, medical director for dementia programs and for clinical programs of the UCLA-Easton Center. In addition to diagnosis and medication reviews, the center’s neurologists order ancillary services as needed, including home-fall and driving evaluations.

Dr. Vossel notes that a combination of extensive neuropsychological testing, patient history, caregiver interviews and state-of-the-art imaging tools, such as high-resolution MRI and FDG-PET, are often required to ensure that patients experiencing early signs of memory loss or other unusual cognitive symptoms are accurately diagnosed. “With high-resolution MRI sometimes we pick up hippocampal sclerosis as the cause of the memory loss. With EEG, we might learn that seizures are the cause. With blood work, we can detect autoimmune diseases or vitamin deficiencies. And some dementias associated with movement disorders can involve subtle features that a neurologist would pick up,” he says. “All of us are being humbled by how challenging proper diagnosis can be.”

Accurate diagnosis and, beyond that, understanding the different presentations within various dementias is important both for tailoring medications and for preparing patients and families for the prognosis, Dr. Vossel explains. “The therapies we have can help a great deal with day-to-day symptoms. Although they do not slow disease progression, they can preserve independence longer,” he says. “But there are also drugs used for memory loss and Alzheimer’s disease that can exacerbate behaviors in frontotemporal dementia, and certain medications should be avoided for patients with Lewy body disease.” In terms of prognosis, he adds, understanding the likely trajectory of the disease can help patients and their families as they consider future plans, as well as point them toward potential measures and support necessary to ensure the patient’s safety as the disease progresses. The UCLA-Easton Center houses a robust research program that includes pharmacological-sponsored and investigator-initiated clinical trials, as well as large NIH-funded observational studies. The studies are open to individuals experiencing symptoms, as well as those believed to be at risk. Through participation in the research, patients can learn more about their disease from sophisticated biomarker imaging of tau and amyloid beta, or from extensive cognitive testing and longitudinal assessments. The center’s researchers also gather spinal fluid, as well as blood and genetic samples, from interested subjects to assess biomarker determinants of future risk in individuals who aren’t experiencing symptoms. Dr. Vossel’s own research centers around his key discovery that as many as 40% of patients with Alzheimer’s disease experience silent seizure activity during sleep that affects their cognition, and an additional 20% can develop overt seizures; his group has begun clinical trials to address and mitigate those seizures, with early evidence that doing so can improve cognitive outcomes. “There’s a great deal we still don’t know about factors causing the disease and what increases individual risk,” Dr. Vossel says. “We hope to recruit diverse research participant pools to obtain answers.”

For more information about the Mary S. Easton Center for Alzheimer’s Disease Research at UCLA, go to: eastonad.ucla.edu
**Multiple treatment options available to patients with epilepsy**

(continued from cover)

a substantial impact on quality of life, he notes, both from the seizure risk and the potential for cognitive impairment and sudden death from epilepsy. Many patients also experience debilitating medication side effects, as well as comorbidities, such as depression and suicidality.

Patients whose epilepsy is not fully controlled by medication should be referred to a comprehensive epilepsy center, where a thorough evaluation can point the way toward a growing array of effective treatment options. Among the key additions to the therapeutic arsenal in recent years are various forms of neurostimulation that may help patients with medication-resistant epilepsy who are either not surgical candidates or prefer a less-invasive approach.

Dr. Stern and center codirector Dawn Eliashiv, MD, recommend that any patient who isn’t seizure-free after one or two medication treatments be referred to a center of excellence such as UCLA. But studies have found that many patients with uncontrolled epilepsy haven’t seen appropriate specialists.

Among the reasons, Dr. Eliashiv notes, is the misconception that specialized centers are only for patients who need surgery. “Many patients fear surgery, and that has served as a barrier for physicians in referring to a comprehensive epilepsy center for evaluation, even though we offer much more than that,” Dr. Eliashiv says.

Often, major interventions aren’t required to improve a patient’s condition. “Sometimes a new medication is all a person needs,” Dr. Stern says. “But we find that many patients worry about experiencing side effects from the change, so they become stuck in their current, inadequate regimens.”

Determining the best course of treatment for each patient starts with a thorough evaluation to pinpoint the diagnosis — a process that generally involves some combination of MRI, PET, EEG and, most importantly, the workup and history-taking of subspecialized clinicians. Dr. Stern points out that in as many as one-third of the patients, such an evaluation may reveal that a patient’s seizures aren’t epileptic, but rather the result of another condition that mimics epilepsy and calls for a treatment other than antiseizure drugs. For patients with epilepsy, a subspecialist with intimate knowledge of the many medications and their side effect profiles can successfully guide the patient to the ideal medical regimen.

For patients found to have medication-resistant epilepsy, the best hope for stopping the disabling seizures is to surgically remove the portion of the brain that is causing them. “Resective surgery is the gold standard in terms of giving people with epilepsy a chance for total seizure freedom, with minimal or no side effects,” says neurosurgeon Assaf Bar, MD, PhD. But Dr. Barí says that, while more patients are surgical candidates than in the past, the majority still are not — in many cases because their seizures originate from areas of the brain that serve critical functions.

For these patients, the UCLA Seizure Disorders Center offers three modalities of neurostimulation, which can reduce seizure risk in a manner that is both less invasive and reversible. Neurostimulation aims to abort the abnormal brain rhythms responsible for the seizures through a device that sends electrical impulses to the brain.

In deep-brain stimulation (DBS), which has been used effectively for patients with movement disorders such as Parkinson’s disease for two decades, the neurosurgeon makes dime-size openings in the skull to place electrodes on either side of the brain. A battery-operated device implanted under the collarbone sends continuous electrical signals to the area of the brain that is believed to propagate the seizures. The UCLA Seizure Disorders Center neurologists identify appropriate candidates and work closely with the neurosurgical team to fine-tune the therapy and manage the patient’s medication after the device is implanted.

Another procedure, responsive neurostimulation (RNS), uses a device that learns how to read brain signals to detect seizures, then stimulates the brain to abort the activity before it becomes a full-blown seizure. For patients who want to avoid any type of brain procedure, vagus nerve stimulation places an electrode around the nerve in the neck that goes to the brain, and indirectly stimulates the brain through a pacemaker-like device implanted in the chest that monitors heart rates as a proxy for seizure activity. “One neurostimulation modality doesn’t exclude using another,” Dr. Barí says. “And it is a modifiable treatment — if it’s not effective or isn’t well tolerated, we can turn the device off and nothing has changed.”

Dr. Stern and Dr. Eliashiv stress that patients referred to the UCLA Seizure Disorders Center see a multidisciplinary team of subspecialists who collaborate with the referring physician to develop and implement a treatment plan individualized to the patient’s needs. “We are relentless in going the extra mile for our patients,” Dr. Eliashiv says. “With so many treatment options, it’s important not to give up.”
Brain cancer has proved to be among the deadliest and most difficult malignancies to treat, with significant hurdles standing in the way of effective radiation and chemotherapeutic approaches. But the UCLA Brain Tumor Center — a National Cancer Institute–designated Specialized Program of Research Excellence (SPORE) — is making headway through a multidisciplinary approach to bringing basic discoveries to fruition for glioblastoma, the most aggressive and lethal brain tumor.

"The SPORE requires something few institutions have — the ability to take projects from bench to bedside within five years," says Linda M. Liau, MD, PhD, chair of the UCLA Department of Neurosurgery and, with Professor of Neurology Timothy Cloughesy, MD, codirector of the UCLA Brain Tumor Center. "It builds a cadre of researchers working together on the same problem, with a focus on getting novel treatments to patients.”

"Every time we test a new treatment, we want to figure out why it’s not working for certain patients and how we can overcome that resistance," adds P. Lea Nghiemphu, PhD, professor of clinical neurology and a basic scientist. Dr. Liau and Robert Prins, MD, PhD, professor of radiation oncology, are the clinical lead in this the project with the basic science lead, Frank Pajonk, MD, PhD, professor of radiation oncology.

The researchers found that in mouse models of glioblastoma, combining the dopamine receptor antagonist trifluoperazine with radiation delayed tumor recurrence, significantly extending survival. In a follow-up study, they added a statin used to lower cholesterol levels and found that, in combination with trifluoperazine and radiation, median survival in mice was extended fourfold compared with radiation alone. Based on those findings, the group is preparing to test these combination therapies in patients with recurrent glioblastoma after standard therapy to see if the strategy inhibits the development of the resistant stem cells.

A third SPORE project is developing new strategies to deliver epidermal growth factor receptor (EGFR)–inhibiting drugs to the brain. EGFR is genetically altered in approximately 60% of glioblastoma tumors, making it a prime target for molecular therapies. Nonetheless, while EGFR antibodies have shown therapeutic success in treating certain breast and lung cancers, they have been ineffective in glioblastoma. "This is largely because these drugs haven’t had good blood–brain-barrier penetration, which has prevented them from getting to the brain at sufficient levels," says Dr. Cloughesy, who also is director of the UCLA Neuro-Oncology Program.

Dr. Cloughesy is collaborating with David Nathanson, PhD, of UCLA’s Department of Molecular and Medical Pharmacology, and Michael Jung, PhD, the UCLA chemist whose laboratory laid the groundwork for the prostate-cancer drugs enzalutamide and apalutamide, on research aiming to develop more brain-penetrant EGFR inhibitors, with one novel drug that is an IND-enabling path and should be available for use in patients in the near future. Meanwhile, Dr. Nathanson’s lab capitalized on the finding that EGFR regulates glucose metabolism to employ PET imaging as a tool to measure the metabolic vulnerabilities in glioblastoma that can potentially be exploited pharmacologically, improving how patients respond to targeted EGFR inhibitors. The researchers are using their newly developed biomarker to look for other potent brain-penetrant EGFR inhibitors.

In all of the UCLA SPORE projects, Dr. Cloughesy says, the common theme is developing ways to overcome resistance to current therapies. "There’s not going to be one cure for glioblastoma," Dr. Liau adds. "It’s going to require a complex interplay of different treatments and stratification of different patients, as we learn which ones work for which type of tumor and which type of patient.”

The SPORE grant currently funds three projects that involve investigator-initiated clinical trials, each co-led by a clinician and a basic scientist. Dr. Liau and Robert Prins, MD, PhD, a basic scientist and professor in the Department of Neurosurgery, are building on seminal work by Dr. Liau’s team that led to the development of a first-of-its-kind personalized cellular vaccine for glioblastoma, which has shown promising results in several earlier phase clinical trials. Brain cancers were widely believed to be immune-privileged — incapable of being attacked by the immune system — until research in Dr. Liau’s lab demonstrated that they’re not the same in every patient,” she says. Using the patient’s own tumor tissue as the antigen source for the vaccine eliminates the need for us to second-guess which proteins to target for each individual patient.”

The next step involves applying lessons learned from the laboratory to improve the vaccine’s efficacy. To that end, the group led by Drs. Liau and Prins launched a trial in 2019 that uses the vaccine in combination with checkpoint inhibitors, based on their laboratory analysis of how tumors in animal models were able to overcome the immunotherapy.

In a second SPORE project, researchers are pursuing novel strategies to block the process, called phenotypic conversion, that occurs when glioblastoma patients receive radiation therapy. "We think the reason tumors grow back and become resistant to radiation is that radiation treatment in itself induces cellular changes in tumor cells that make them stem-like and capable of regrowth,” says Dr. Nghiemphu, who is the clinical lead in this the project with the basic science lead, Frank Pajonk, MD, PhD, professor of radiation oncology.

The UCLA Brain Tumor Center takes multidisciplinary approach to attacking glioblastoma

UCLA has developed state-of-the-art MRI and PET imaging techniques and novel analysis tools to better understand the physiological and metabolic changes that occur within a patient’s brain tumor before, during, and after treatment. (Image Courtesy of Dr. Ben Ellingson/UCLA Department of Radiology.)
Comprehensive care following stroke is vital to fullest possible recovery

Emergency treatment for stroke is essential to save lives and preserve function, but follow-up care is vital to ensure the fullest possible recovery. “Stroke patients need to be seen over time after the acute event,” says David Liebeskind, MD, director of the UCLA Stroke Center. At UCLA, “we develop ongoing partnerships with community physicians to provide expertise and ensure that their patients receive the long-term follow-up that will optimize outcomes.”

The UCLA Stroke Center provides comprehensive diagnostic and therapeutic care for simple and complex vascular disorders through multidisciplinary teams that work closely with patients and their referring physicians. “We offer the expertise not just of individuals, but of our center as a whole,” says UCLA neurosurgeon Geoffrey Colby, MD, PhD. “A good part of the success of the procedures we perform comes from the care that’s provided before and after, through the immediate recovery period and beyond.”

In many cases, it pays to not wait for an acute event. For example, when a patient is found to have intracranial atherosclerotic disease (ICAD) — the narrowing of the large vessels of the arteries leading to the brain, putting them at risk for stroke — early referral to an expert center is important, in part because the best course of therapy isn’t always clear.

Beyond managing patients, the center advances clinical care as a leader in research. Dr. Liebeskind heads a number of ICAD studies to learn more about stroke risk and the impact on cognitive function. Using detailed longitudinal imaging studies, for example, his group is examining how physical activity affects blood pressure and other risk factors to prevent stroke. Through computational fluid dynamics, he and his colleagues are learning how the specific architecture of the narrowing of the vessels might affect stroke risk. Dr. Liebeskind also heads a large NIH-funded study of patients with asymptomatic carotid disease to better understand how blood flow relates to cognition over time, and the potential impact on dementia risk.

“The center’s neurosurgeons treat patients with complex vascular lesions, often using revascularization to avert ischemia and then following patients at all stages of the disease. One example of this approach is for Moyamoya disease, a rare, progressive cerebrovascular condition that is one of the primary causes of stroke in children and young adults. “These are usually young people, and often children, who are seemingly healthy; then they suffer a stroke and are at high risk for strokes in the future,” says neurosurgeon Anthony Wong, MD, who specializes in cerebrovascular, pediatric and complex cranial-base surgeries. “Our goal is to correct the chronic lack of oxygenation to the brain, and prevent that damage from occurring for the rest of that individual’s life.”

“We’ve learned a great deal through studies showing that having the full arsenal of surgical techniques is important, given that these patients present differently, and that certain presentations or anatomies respond better to certain treatments,” Dr. Colby adds.

Stroke is rare in the overall pediatric population, and the UCLA Stroke Center stands apart for being staffed with experienced neurologists, neurosurgeons and radiologists who subspecialize in treating pediatric stroke, both in the acute and outpatient settings. “It can be challenging to recognize the signs of stroke in children, as the overall incidence is low and the clinical presentation can be nonspecific, particularly in infants,” neurologist Latisha Sharma, MD, says. Once the acute care is completed, access to a team with a multifaceted approach to outpatient treatment of the child in ensuing years plays an essential role in his or her recovery, Dr. Sharma says.

Although stroke is the third-leading cause of death among women in the United States, Dr. Sharma notes that the symptoms can be subtle and are more likely to be missed or minimized by women than men. “We need to do more to educate women to call 911 and not delay seeking treatment especially if you offer everything and don’t have any biases about one solution for each patient. “We have multidisciplinary conferences that include specialists in neurosurgery, neuroradiology and cerebrovascular neurology in which we make sure our patients receive optimal management,” Dr. Colby says. “The only way you can do that is if you offer everything and don’t have any biases about one procedure or another.”

STORY HIGHLIGHTS

UCLA Stroke Center provides comprehensive diagnostic and therapeutic care for simple and complex vascular disorders.

In addition to adults, the UCLA Stroke Center includes neurologists who are experienced in treating pediatric stroke, both in the acute and outpatient settings.

For more information about the UCLA Stroke Center, go to: uclahealth.org/stroke
Major advances in spine surgery — from minimally invasive techniques to complex spinal deformity procedures — have opened the door for a much wider group of patients suffering from the often-debilitating pain associated with spinal conditions to receive care at specialized centers. Through a multidisciplinary collaboration of specialists in neurosurgery, orthopedics and physiatry, the UCLA Spine Center is optimizing the care of patients who might not have been eligible for surgical care at other centers. Minimally invasive spinal surgery has become an increasingly important part of the armamentarium over the last decade, says Langston Holly, MD, professor and vice chair of clinical affairs for the UCLA Department of Neurosurgery and codirector of the UCLA Spine Center. Minimally invasive spine surgery is initially developed for patients with degenerative disc disease. But over time, minimally invasive techniques have evolved for patients with other spinal pathologies, including tumors and trauma.

"Just as general surgery took large, fairly morbid open procedures and turned them into laparoscopic procedures with fewer complications and shorter hospital stays and recovery times, we have been able to do that with spine surgery through techniques that have improved every year," Dr. Holly says. Often, patients are able to go home within a few hours after a surgery that would have previously required one or more nights in the hospital.

Minimally invasive spinal surgery aims to reduce the amount of soft-tissue dissection and disruption of anatomical structures. "The larger the surgery, the longer the injury takes to heal, and in some cases there can be permanent muscle injury related to the approach to getting down to the spine," Dr. Holly explains. "We are now able to make much smaller incisions, and in most cases we can go between muscle fibers, using a device to create a pathway through a small access corridor down to the spine. Once that device is removed, the muscle falls back into place, and it usually takes just one or two stitches to close.”

Dr. Holly notes that the minimally invasive approach is particularly important for spine patients because many have been on pain medications and may be more sensitive to postoperative pain. "We can decrease their medication use after surgery and get them back to work quicker, and the outcome is often better," he says. Another benefit of the minimally invasive approach is that it allows the surgeon to preserve supporting structures and maintain the integrity of the spine, reducing the chances of the patient needing additional surgery at a later time.

"With more people wanting to maintain an active lifestyle into their 70s and 80s, we’re seeing much greater demand for spine surgery in older patients.”

The surgeries performed by Dr. Vivas and his colleagues have a low margin for error. Historically, Dr. Vivas notes, spinal deformity corrections had unacceptably high rates of complications, including paralysis, and so the surgeries were mostly avoided. But over the past three decades, the technology has greatly improved — in particular, the ability to closely follow the function of the spinal cord during surgery through intraoperative neuromonitoring and various minimally invasive techniques used to augment the deformity surgery.

"There are challenging cases, and in order to have good quality-of-life outcomes, it’s critical to minimize the amount of blood loss and the potential for neurological injury,” Dr. Vivas says. "But if we’re able to do these surgeries safely and with low perioperative morbidity and rates of complication, we can dramatically improve patients’ quality of life, with significant improvements in pain, self-image scores, patient satisfaction, mental health scores and overall function.” The significant advances in safety and outcomes have changed the eligibility calculus, to the point that large-scale spinal deformity surgery is being performed on many patients well into their 70s and 80s. Dr. Vivas notes. Dr. Vivas’ practice also includes a substantial number of revision spine surgeries, another highly specialized procedure for patients who have in many cases suffered for years with their spines fused in a painful position. As with the other procedures, successful surgery requires the type of multidisciplinary approach featured at the UCLA Spine Center. "We offer state-of-the-art care for every subdiscipline of spine surgery," Dr. Vivas says. "And we work together as neurosurgeons, orthopaedists, anesthesiologists and physiatrists, all in close consultation, to take care of patients every step of the way.”

"With more people wanting to maintain an active lifestyle into their 70s and 80s, we’re seeing much greater demand for spine surgery in older patients.”
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