General Introduction to Epilepsy

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KEYWORDS

• Epilepsy • Seizure • Epilepsy surgery • Neuromodulation • Antiseizure medication

KEY POINTS

- Epilepsy affects 50 million globally, with risks including injury and stigma.
- Classified as generalized or focal, with wide-ranging causes including structural, genetic, metabolic, inflammatory and infectious etiologies
- Diagnosis most often relies on history, electroencephalography, and MR imaging; advanced tests are used for drug-resistant cases.
- Treatment primarily involves antiseizure medications, with surgery or neuromodulation for resistant epilepsy.
- Surgical options include resection and neuromodulation devices such as vagus nerve stimulation, deep brain stimulation, and responsive neurostimulation.

INTRODUCTION

Epilepsy is defined by the tendency to have unprovoked seizures[1] and is one of the most common neurologic diseases worldwide. The World Health Organization estimates that 50 million people live with epilepsy, with 49 to 139 new diagnoses per 100,000 people every year.[2] Uncontrolled epilepsy increases the risk for accidental injuries,[3] seizure-related deaths, including sudden unexpected death in epilepsy,[4] cognitive decline,[5] and loss of independence often related to driving restrictions.[6] Stigma attached to epilepsy also remains a significant issue in some parts of the world, resulting in isolation from society for many people.[7] Early diagnosis and effective management are important to mitigate negative impacts on both physical and emotional well-being.

CLASSIFICATION AND CAUSES

Classifying a person's epilepsy is important as it has significant implications for both medical and surgical therapies. Broadly, epilepsy may be classified into generalized or focal.[8] Seizures associated with generalized epilepsies start widely distributed in both cerebral hemispheres. Multiple different seizure types may be generalized at onset, including absence, myoclonic, tonic-clonic, atonic, and tonic seizures. Generalized epilepsies are genetically based, whether that be from a single gene mutation, interactions between multiple genes, or epigenetic factors.[8] It is important to distinguish that a genetic etiology in these cases does not specifically mean inherited as de novo mutations are common.

Seizures in focal epilepsies start in a single area and may spread to other areas.[8] Focal seizures may present with any number of signs and symptoms depending on the location of seizure onset and spread pattern, and the functions associated with those areas (**Box 1**). Focal epilepsies may be caused by any number of etiologies, including congenital structural brain disease (eg, cortical dysplasia), acquired structural disease (eg, traumatic brain injury), genetic predispositions, infection (eg, neurocysticercosis), or autoimmune disease.[8] In many cases, the cause is unknown.

Epilepsies with specific characteristics, such as seizure types, age of onset, electroencephalography (EEG) patterns, and other clinical findings, may be further classified into syndromes.[8]

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Abbreviations

ATLAH	amygdalohippocampectomy
ASM	antiseizure medication
DBS	deep brain stimulation
CAE	childhood absence epilepsy
CT	computed tomography
EEG	electroencephalography
EMU	epilepsy monitoring unit
HARNESS	Harmonized Neuroimaging of Epilepsy Structural Sequences
JAE	juvenile absence epilepsy
MEG	magnetoencephalography
MSI	magnetic source imaging
PET	positron emission tomography
RNS	responsive neurostimulation
SPECT	single-photon emission computed tomography
VNS	vagus nerve stimulation

Identifying a specific epilepsy syndrome can aid in a better understanding of prognosis, treatment strategies, and, in some cases, etiology. An example of the importance of this is highlighted by juvenile absence epilepsy (JAE) and childhood absence epilepsy (CAE). They may present similarly, as both present with absence seizures in childhood and are associated with generalized discharges on EEG and normal brain anatomy. CAE usually presents at an earlier age and with more frequent absence seizures compared to JAE, whereas JAE is also more likely to have tonic-clonic seizures in addition to absence seizures. Accurate syndrome identification based on these differences is important as it impacts prognosis and treatment consideration significantly. CAE is expected to be age-limited in most cases, so counseling can provide reassurance that seizures will likely stop as the child ages and will likely be able to stop seizure medications. JAE, on the other hand, is not reliably age-limited, so expectations can be set early that lifelong treatment may be needed and the medications used to treat should be those effective against both absence and tonic-clonic seizures.[9]

Whether generalized or focal, epilepsy can also be classified as drug-resistant if certain criteria are met. Drug-resistant epilepsy is defined as continued seizures despite treatment with at least 2 appropriately selected medications at reasonable doses, either alone or in combination.[10] This definition is based on studies reliably showing that approximately two-thirds of patients will be seizure-free on some dose of one of the first two antiseizure medications used. Following that, the odds of seizure-freedom are low.[11,12] Recognizing drug resistance is important as surgery or neuromodulation devices may be appropriate for treatment in addition to ongoing medication therapy. All people with drug-resistant epilepsy should be offered a surgical evaluation focused on these therapies.

Box 1
Basic signs and symptoms of a focal seizure based on the location of onset

Temporal lobe

- Déjà vu
- Epigastric rising
- Automatisms (repetitive movements)
  - Purposeless or semi-purposeful hand movements
  - Lip smacking
  - Tongue thrusting

Frontal lobe

- Sleep-related seizures
- Hyperkinetic movements
- Asymmetric tonic stiffening
- Onset with spreading clonus ("Jacksonian march")

Operculum

- Isolated face motor symptoms (clonus or tonic stiffening)
- Throat sensations—choking or constriction
- Gagging

Occipital lobe

- Vision changes isolated to a single hemifield
- Unformed visual phenomena—for example, flashes, colors, flickering
- Disruption of vision in hemifield

Parietal lobe

- Simple sensory phenomena—for example, paresthesias, numbness, pain (rare)
- Complex sensory phenomena—for example, perceptual illusions of own body or external environment

EVALUATION

Early evaluation often revolves around risk-stratification of future seizures after a single first-time seizure or epilepsy classification if the clinical diagnosis is already secure based on recurrent unprovoked seizures. If seizures continue despite reasonable attempts at treatment, then additional evaluation should be performed aimed at surgical and neuromodulation treatment strategies. Testing

performed is ultimately dependent on the goals of evaluation.

History and Physical Examination

Clinical history is the cornerstone of any seizure or epilepsy evaluation. A seizure may be perceived as "first-time," particularly if it is a tonic-clonic seizure due to its conspicuous appearance, but careful history taking can disclose other events suggestive of prior seizures that would result in a diagnosis of epilepsy prior to testing. For instance, myoclonic seizures or subjective symptoms experienced only by the patient, such as déjà vu and epigastic rising sensations, may not be recognized as abnormal without direct questioning. Epilepsy can be diagnosed if the clinical history is strongly suggestive of prior unrecognized seizures, making treatment appropriate regardless of test results.

Physical examination findings are also important in assessing risk for future seizures after a first-time seizure. Abnormal examination findings suggestive of central nervous system dysfunction or disease denote an increased risk of future unprovoked seizures and could support treatment after a first-time seizure.[13] In some patients with progressive neurologic diseases that have seizures as a symptom, serial examinations may also be useful in documenting disease progression.

Electroencephalography

EEG measures electrical brain potentials and provides a graphical representation for review. Scalp EEG may be performed as a time-limited outpatient study, most commonly 20 to 60 minutes, in a lab setting or as a long-term study for one or more days using ambulatory EEG or in an inpatient setting. Epileptiform abnormalities on EEG help define risk of future seizures and classify type of epilepsy.[14] The most common epileptiform abnormalities are generalized spike and wave discharges and focal spikes or sharp waves (**Fig. 1**). The presence of these abnormalities after a first-time seizure signifies an increased risk for future seizures,[13] while the location (generalized or focal) defines the type of epilepsy.[14]

In drug-resistant epilepsy, long-term EEG monitoring is employed to record seizures to confirm an epilepsy diagnosis and localize seizures for consideration of advanced therapies. This EEG monitoring is usually performed over several days in specialized inpatient epilepsy monitoring units (EMUs) where staff training and unit accommodations optimize safety for the capture of seizures. Seizure medication reduction and employing seizure triggers are commonly performed methods to elicit seizures in the EMU setting as a spontaneous seizure may not reliably occur within the time limitations of the monitoring. In some patients, additional seizure monitoring with intracranial EEG using either stereotactically placed EEG electrodes (called stereo-EEG) or electrode grids and strips is required for more precise localization.

Imaging

Anatomic imaging is useful when assessing first-time seizure or epilepsy. Advanced imaging techniques are generally reserved for the evaluation of drug-resistant epilepsy.

Structural brain imaging with MRI is an integral part of epilepsy evaluations.[15] In early evaluations, certain structural abnormalities confer a high risk for unprovoked seizures and serve to support empirical treatment following a first-time seizure. Anatomic lesions are also important to identify in drug-resistant patients when present because they confer the highest likelihood for success if epilepsy surgery can be safely performed compared to "nonlesional" or MR imaging-negative epilepsies.[16] If anatomic lesions are present but unidentified, care teams run the risk of undertreatment, which may be failing to start medical therapy after a first-time seizure or failing to offer what would otherwise be appropriate surgical interventions in someone with drug-resistant epilepsy. Common anatomic abnormalities in focal epilepsies include mesial temporal sclerosis, temporal lobe encephaloceles, long-term epilepsy-associated tumors (eg, dysembryoplastic neuroepithelial tumors), cavernous hemangiomas, encephalomalacia, and focal cortical dysplasias.

Epilepsy-focused MR imaging should be performed with certain techniques. The International League Against Epilepsy recommends a standardized Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MR imaging) protocol as a minimum standard for anatomic MR imaging in epilepsy (**Box 2**).[15] These minimum criteria allow for high-quality views of the brain's entire anatomy in any plane, limits the partial volume effect, and can be performed even on 1.5T scanners. Although these criteria can be achieved on some 1.5T scanners, 3T MR imaging is preferable when possible, due to superior image quality. Ultrahigh field MR imaging systems such as 7T MR imaging are increasingly available for clinical use, currently at more than 60 centers globally, and may detect additional abnormalities beyond conventional field strength MR imaging.[17]

Computed tomography (CT) may be useful in certain circumstances. CT is the first-line of assessment acutely following a first-time seizure to evaluate for significant intracranial pathology.

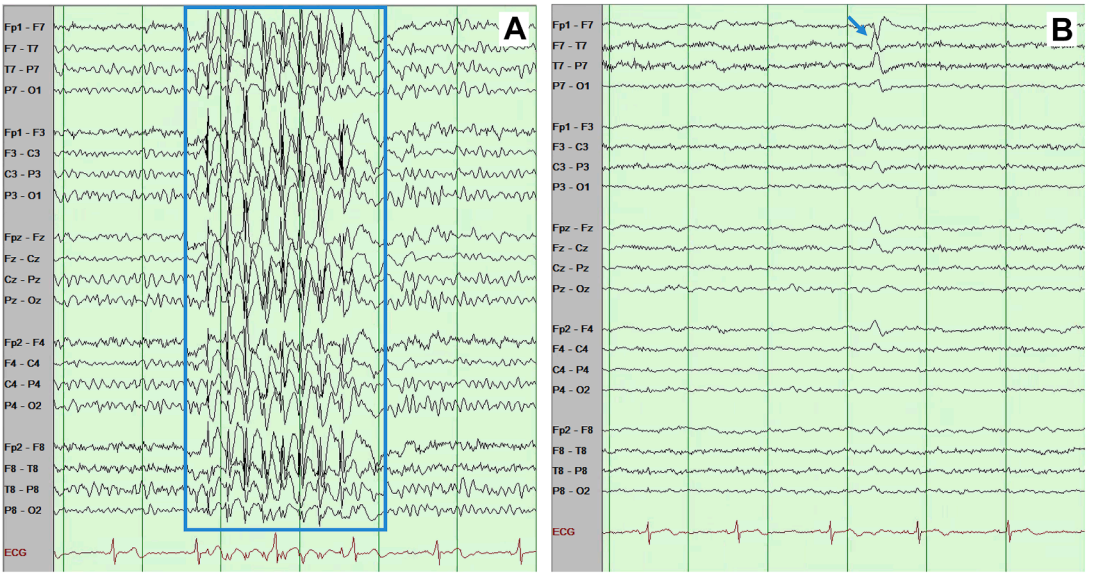

Fig. 1. An example of an (A) epileptiform generalized spike and wave discharge (box) and (B) focal left fronto-temporal sharp wave discharge (*arrow*).

Non-acutely, skull base CT can be helpful to evaluate for bony defects resulting in encephaloceles that may be epileptogenic if MR imaging is equivocal.

Nuclear and functional imaging can also be useful in the evaluation of drug-resistant focal epilepsy. Positron emission tomography (PET), either CT- or MR imaging-based, can highlight areas of hypometabolism associated with the region of seizure-onset (**Fig. 2**).[18] Single-photon emission computed tomography (SPECT) can be used to identify seizure onset through subtraction of ictal and interictal scans overlayed on MR imaging (subtraction ictal SPECT co-registered to MR imaging or SISCOM) and can utilize statistical parametric mapping to further refine localization (statistical ictal SPECT co-registered to MR imaging or STATISCOM).[19] Functional MR imaging can lateralize language, locate important functional

Box 2
Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MR imaging) protocol

High-resolution 3D T1-weighted (MP-RAGE, spoiled gradient echo, or turbo field echo protocols) at millimetric voxel resolution ($1 \times 1 \times 1$ mm^3)

High-resolution 3D fluid-attenuated inversion recovery (FLAIR) at millimetric voxel resolution ($1 \times 1 \times 1$ mm^3)

High in-plane resolution 2D coronal T2-weighted at submillimetric voxel resolution ($0.4 \times 0.4 \times 2$ mm^3)

No interslice gaps

May be completed with T1 gadolinium and susceptibility-weighted imaging/T2* if tumor, vascular malformation, or infectious etiologies are suspected

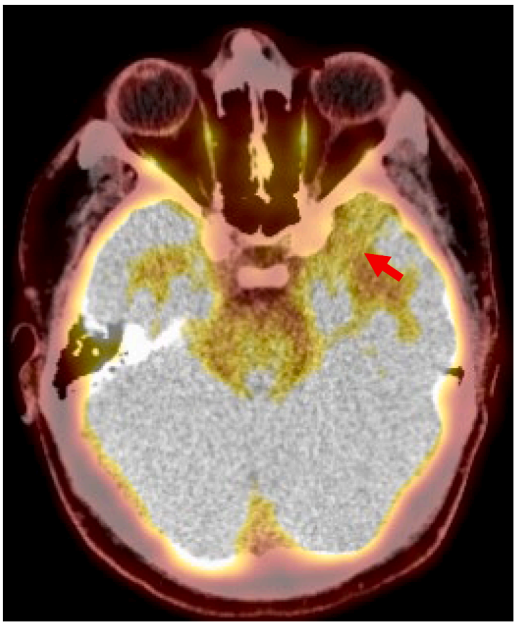

Fig. 2. Left anterior temporal PET hypometabolism (*arrow*) in a patient with focal epilepsy and recorded left temporal seizures.

areas, and may assess memory function that can be integrated into decision making when considering risks of epilepsy surgery.[20]

Other Testing

Lab investigation is important in the acute evaluation of first-time seizures to eliminate significant metabolic derangements or other exogenous factors as a cause for a provoked (rather than unprovoked) seizure. In established epilepsy, most lab testing has limited utility in assessing seizure etiology. Genetic testing either through epilepsy panels or whole exome or genome sequencing may reveal an etiology in some people and is recommended in all people with unexplained epilepsy.[21]

Autoimmune evaluations may also be appropriate in certain situations. Many people with autoimmune encephalitis present acutely with active inflammation and multiple neurologic symptoms. This can result in epilepsy long-term even after adequate treatment of acute inflammation. Others can have an entirely outpatient presentation, including LGI1 encephalitis (with characteristic faciobrachial dystonic seizures) and GAD65-associated epilepsy.[22]

Magnetoencephalography (MEG) is another neurophysiology-based method of recording brain potentials to identify epileptiform abnormalities. It is complementary to EEG, and most often used in surgical evaluations. MEG is combined with magnetic source imaging (MSI) to co-register MEG dipoles on brain MR imaging to localize potential areas of seizure onset.[23]

TREATMENT

Epilepsy can be treated with medications, surgery, stimulation devices, and non-medical and non-surgical therapies. While treatment is often modified based on individual patient factors, there are general principles used across all epilepsies to some degree that help guide treatment paths.

Antiseizure Medications

Treatment with antiseizure medications (ASMs) is a mainstay for any epilepsy. ASMs can be classified into broad spectrum and narrow spectrum medications (**Table 1**). Broad spectrum medications are useful for many seizure types in both generalized and focal epilepsies. Narrow spectrum ASMs have a smaller focus of utility for certain seizure or epilepsy types. While many medications have a defined spectrum, emergence of new data over time can expand the spectrum of an ASM.[24]

The general approach to epilepsy treatment with ASMs is a mix of dosing and time. The first medication is started at a low dose. If seizures recur, then the dose is increased and observation for recurrence is continued. If seizures continue to recur despite escalating doses of the first medication, then a second ASM can be used to replace the first ASM or added to it if there was a clear beneficial effect of the first drug. The same process is then performed with the second ASM, as well as future ASMs if seizure-freedom is not achieved. This can be frustrating to patients as the appearance is that their neurologist "doesn't know what to do" and is just "guessing." Unfortunately, the truth is not far from perception even under the best circumstances as there is no single "best" medication for most people. Some factors outlined below can help create more specific treatment plans for some people.

Table 1
Defined Spectrum of Common Antiseizure Medications

Broad Spectrum	Narrow Spectrum
Benzodiazepines (clonazepam, clobazam, etc.)	Carbamazepine
Lamotrigine	Eslicarbazepine
Levetiracetam	Ethosuximide (absence seizures only)
Perampanel	Lacosamide
Topiramate	Oxcarbazepine
Valproic acid	Phenobarbital
Zonisamide	Phenytoin

Deciding which ASM to use is guided by patient factors and epilepsy information. However, some data may be limited early on. If someone has had only a few seizures that do not have specific features and testing with EEG and MR imaging are unremarkable, then there may not be enough information to know if the epilepsy is generalized or focal. In these cases, ASMs that are generally well-tolerated, easy to start, readily available, and have limited pharmacokinetic and pharmacodynamic complexities are typically used.

ASM selection can also be guided by medical comorbidities, which may result in favoring or avoiding certain medications in specific instances. Migraine is a common comorbidity where epilepsy treatment with topiramate or valproic acid may provide therapy for both conditions. Some mood disorders may benefit from a mood stabilizing ASM like lamotrigine, carbamazepine, or valproic acid for epilepsy treatment in addition to appropriate mental health care. Conversely, avoiding certain ASMs that are known to commonly have

mood side effects, such as levetiracetam and perampanel, may be considered in people with a significant psychiatric history. Topiramate and zonisamide may be avoided in people who have a history of kidney stones as their carbonic anhydrase activity creates a favorable metabolic environment for stone formation.[24]

There are also demographic factors that can guide ASM considerations. People with childbearing potential are a significant portion of the epilepsy population. Working around family planning is important in this group as no ASM is entirely safe during pregnancy. If planning for pregnancy the treating neurologist should be actively involved so that ASMs can be tailored as much as possible to the lowest dose, safest, and most effective for that person's epilepsy. It is recommended that all people with childbearing potential who are not attempting pregnancy have an effective form of contraception. Regardless of plans for pregnancy or use of contraception, all people with childbearing potential are also recommended to take folic acid to help potentially prevent teratogenic effects of ASMs in the event of a pregnancy.[25]

Surgical and Invasive Neuromodulation Therapies

Epilepsy surgery or neuromodulation therapies may be an option to eliminate or significantly reduce seizure burden for people who have drug-resistant epilepsy. All people with drug-resistant epilepsy should be offered a surgical epilepsy evaluation to consider which treatments may be most appropriate.

Destructive surgeries

Surgical options include destructive procedures to remove, disconnect, or ablate the area or areas of seizure onset. Destructive epilepsy surgeries are performed following extensive evaluations to understand a patient's type of epilepsy, location of seizure onset, and the balance of the potential for seizure freedom versus neurologic deficits if the area is operated on. Most destructive epilepsy surgeries are aimed at seizure-freedom; however, some surgeries, like corpus callosotomy, are expected to be non-curative. Even surgeries that are typically used with an intent to achieve seizure freedom, like an anterior temporal lobectomy with amygdalohippocampectomy (ATLAH), can be considered to help reduce seizure burden with a non-curative intent if it is felt to be safe to perform, reasonably likely to improve quality of life, and prevent significant seizure-related morbidity.

ATLAH and mesial temporal MR-guided laser interstitial thermal therapy are 2 of the most common surgical procedures performed to treat epilepsy. Other surgeries include resection of focal epilepsy-causing lesions or cortical areas, severing of the corpus callosum through callosotomy, or disconnection of a portion of brain (eg, posterior disconnection) or entire hemisphere via hemispherotomy.

Invasive neuromodulation

Some patients will not be candidates for a destructive surgical procedure or may elect not to pursue a destructive surgical intervention. Neuromodulation therapies with invasive stimulation devices can be used to help control seizures in these cases. Neuromodulation techniques are not anticipated to be curative in most people and do not replace the need for ASM management, although small numbers will achieve long-term remission or very long intervals between seizures.[26] Invasive neuromodulation is applied through vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS).

VNS is the oldest neuromodulation therapy approved for the treatment of epilepsy. VNS provides open-loop stimulation to the vagus nerve which feeds back to the central nervous system to reduce seizure tendency. There are several hypotheses to the mechanism of VNS in seizure reduction, but the precise mechanism is not defined. The entire VNS system is contained outside of the central nervous system, with the impulse generator placed in the chest and leads tunneled to electrodes on the vagus nerve.[26]

DBS is an open-loop stimulation system that targets the thalamus. Currently, the only approved target is the anterior nucleus of the thalamus in the United States. Similar to VNS, DBS systems provide ongoing stimulation to their target areas to modulate the seizure network and reduce seizure burden. While the electrodes are within the thalamus, the DBS generator is placed in the chest with leads tunneled under the skin.[26]

Unlike either VNS or DBS, the RNS system is a closed-loop stimulation system. Electrodes are placed within the brain around the area of seizure onset. When the device senses the start of an electrographic seizure then electrical stimulation is applied to terminate the seizure, ideally before the patient experiences any symptoms or impairment. The impulse generator for RNS is contained within a cradle that is placed in a surgically created skull defect.[26]

PUTTING IT ALL TOGETHER: A COURSE OF EVALUATION AND TREATMENT

With and understanding of evaluation and treatment strategies, we can review a timeline of how both progress in parallel over a timeline looking

at first-time seizure, newly diagnosed or established epilepsy, and drug-resistant epilepsy.

First-Time Seizures

Approximately 10% of all people will have a single seizure for any reason at some point in their life, but only 1% to 2% will go on to develop epilepsy.[27] Studies evaluating empirical treatment after any first-time seizure showed that this strategy resulted in overtreatment, no quality of life improvement, and did not produce a better treatment response compared to waiting for a second seizure in people who were deemed low risk.[28,29] Therefore, it is important to identify who would benefit from early treatment and who may be appropriate to observe without treatment after a single seizure.

Emergent inpatient evaluation for first-time seizures at minimum should include CT head to evaluate for acute or previously undiagnosed intracranial pathology. Laboratory tests should include a complete blood count and metabolic panel to evaluate for provoking causes. Drug screening should also be considered. If there is specific concern for meningitis or encephalitis based on clinical findings such as fever or encephalopathy with failure to recover after seizure then lumbar puncture can also be performed. If acute testing is negative and the patient recovers, additional evaluation can take place as an outpatient. Prophylactic treatment with an ASM does not need to be routinely provided at this stage if there are no apparent risk factors.

As an outpatient, a detailed history and examination should be performed by a neurologist. Testing with brain MR imaging utilizing an epilepsy-specific protocol is recommended as standard MR imaging protocols may not identify epileptogenic lesions readily due to subtlety. A routine outpatient EEG should also be performed. A 24 hour ambulatory EEG can be considered following first-time seizure if a routine EEG is non-diagnostic. If the evaluation is negative, then the patient can be observed without treatment. Starting an ASM would be appropriate if one or more additional unprovoked seizures occur or if evaluation showed findings that put the patient at risk of having future unprovoked seizures.

Newly Diagnosed or Established Epilepsy

Those who have first-time seizures with significant risk factors or have multiple unprovoked seizures meet diagnostic criteria for a diagnosis of epilepsy.[1] If history and diagnostic testing suffice for epilepsy classification, then treatment can be applied using an appropriate spectrum of medication aimed at the type of epilepsy. Individual patient factors, like medical comorbidities and childbearing potential, should also be considered in ASM selection.

If epilepsy is clinically supported by recurrent seizures but history and initial diagnostic testing are inadequate to define the type of epilepsy, then a broad-spectrum medication can be used and continued evaluation performed to help aid in tailoring therapy long-term.

If the initial MR imaging was not performed with an epilepsy-specific protocol, then it should be repeated to ensure subtle abnormalities are not missed. If there are equivocal imaging findings that may suggest a lesion, then additional imaging studies to provide diagnostic clarity are appropriate. Genetic and autoimmune evaluations may also be appropriate in some circumstances if an etiology is not otherwise identified. Patients with genetic epilepsy syndromes may frequently have unremarkable brain MR imaging examinations. Some genetic epilepsy syndromes are associated with malformations of cortical development, white matter signal abnormality, and/or brain parenchymal volume loss.[30] Patterns of imaging findings on MR imaging and PET have been described with some autoimmune epilepsy diagnoses.[31]

In the case of a non-diagnostic initial EEG, a repeat EEG may also be useful. Only approximately 50% of people with epilepsy will have an abnormal EEG on their first study, but that number rises to between 70% and 90% over the course of 4 or 5 outpatient EEGs.[32,33] Long-term outpatient monitoring using ambulatory EEG for 24 to 48 hours also increases the yield of epileptiform abnormalities.[34]

Regardless of the outcome of the ongoing diagnostic evaluation at this stage, ASMs should continue to be adjusted based on clinical seizure recurrence. If escalating doses of an initial ASM fail to result in seizure freedom, then a second ASM should be tried, either in combination or as an exchange with ongoing dose adjustments if seizures continue. If a second ASM fails at reasonable doses, then the patient should be classified as drug-resistant[10] and considered for a surgical evaluation.

Drug-resistant Epilepsy

In drug-resistant epilepsy, evaluation is focused on precisely defining the epilepsy type and, if applicable, localizing seizure onsets to understand what surgical or neuromodulation therapies may be most appropriate. This includes EMU monitoring to document typical seizures on EEG, advanced imaging techniques, neuropsychology assessments to consider cognitive risks, and

potentially additional neurophysiologic information with MEG if available. Select patients may be able to move straight to a destructive surgery if data are highly concordant with the clinical history, with good odds at seizure freedom and low risk from a potential epilepsy surgery. This most often applies to patients with MR imaging-visible lesions in anatomically safe locations. In patients where the precise localization of seizures is still in question or there are concerns about the potential for neurologic deficits related to surgery, additional evaluation with intracranial EEG is often performed. Some patients may move directly to a neuromodulation device without intracranial monitoring if the non-invasive evaluation shows unfavorable surgical candidacy, such as multiple areas of independent seizure onset.

ASM management can continue to be performed in parallel to a surgical evaluation as some patients will become seizure-free with additional medication attempts.

SUMMARY

Epilepsy is a common and complicated disease. Evaluation and treatment strategies are focused on both individual patient characteristics and epilepsy type. EEG and imaging are instrumental in classifying epilepsy and can help inform the most effective treatment strategies. ASMs are able to effectively make most people with epilepsy seizure-free. Epilepsy surgery or invasive neuromodulation can help treat epilepsy in those who are drug-resistant.

CLINICS CARE POINTS

- Treatment should be offered to anyone who has had 2 or more unprovoked seizures, or who has had 1 unprovoked seizures and significant risk factors for future unprovoked seizures.
- Anyone with epilepsy who has failed 2 or more appropriately selected and dosed antiseizure medications should be offerred a surgical evaluation for more advanced epilepsy treatment.
- Surgical evaluations include consideration for neuromodulation devices (VNS, DBS, and RNS), so even if someone does not seem like a good candidate for a destructive surgery they can still benefit from a surgical evaluation.

DISCLOSURES

Dr D.B. Burkholder, Dr B.J. Burkett, and Dr R.E. Watson have no conflicts of interest.

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(4):475–82.
2. Epilepsy: a public health imperative. World Health Organization; Geneva, 2019. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/epilepsy-a-public-health-imperative. Accessed July 1, 2025.
3. Asadi-Pooya AA, Tomson T. A reappraisal of injuries and accidents in people with epilepsy. Curr Opin Neurol 2021;34(2):182–7.
4. Shlobin NA, Thijs RD, Benditt DG, et al. Sudden death in epilepsy: the overlap between cardiac and neurological factors. Brain Commun 2024;6(5):fcae309.
5. Rayner G, Tailby C, Jackson G, et al. Looking beyond lesions for causes of neuropsychological impairment in epilepsy. Neurology 2019;92(7):e680–9.
6. Kang JY, Mintzer S. Driving and epilepsy: a review of important issues. Curr Neurol Neurosci Rep 2016;16(9):80.
7. Kwon CS, Jacoby A, Ali A, et al. Systematic review of frequency of felt and enacted stigma in epilepsy and determining factors and attitudes toward persons living with epilepsy-Report from the International League against Epilepsy Task Force on Stigma in Epilepsy. Epilepsia 2022;63(3):573–97.
8. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for classification and terminology. Epilepsia 2017;58(4):512–21.
9. Guerrini R, Marini C, Barba C. Generalized epilepsies. Handb Clin Neurol 2019;161:3–15.
10. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia 2010;51(6):1069–77.
11. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342(5):314–9.
12. Chen Z, Brodie MJ, Liew D, et al. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol 2018;75(3):279–86.
13. Berg AT. Risk of recurrence after a first unprovoked seizure. Epilepsia 2008;49(Suppl 1). https://doi.org/10.1111/j.1528-1167.2008.01444.x.
14. Smith SJM. EEG in the diagnosis, classification, and management of patients with epilepsy. J Neurol Neurosurg Psychiatry 2005;76(Suppl 2):ii2–7.
15. Bernasconi A, Cendes F, Theodore WH, et al. Recommendations for the use of structural magnetic resonance imaging in the care of patients with epilepsy: a consensus report from the International

League against Epilepsy Neuroimaging Task Force. Epilepsia 2019;60(6):1054–68.
16. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. JAMA 2015;303(3):285–93.
17. Opheim G, van der Kolk A, Markenroth Bloch K, et al. 7T epilepsy task force consensus recommendations on the use of 7T MRI in Clinical Practice. Neurology 2021;16(96):327–41.
18. Courtney MR, Antonic-Baker A, Chen Z, et al. Association of localizing 18F-FDG-PET hypometabolism and outcome following epilepsy surgery: systematic review and meta-analysis. Neurology 2024;102(9):e209304.
19. Kazemi NJ, Worrell GA, Stead SM, et al. Ictal SPECT statistical parametric mapping in temporal lobe epilepsy surgery. Neurology 2010;74(1):70–6.
20. Gross WL, Swanson SJ, Helfand AI, et al. FMRI in anterior temporal epilepsy surgery FATES study. Predicting memory decline from left temporal lobe epilepsy surgery using preoperative fMRI: a multicenter study. Neuroimage Clin 2025;46:103804.
21. Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: an evidence-based practice guideline of the national society of genetic counselors. J Genet Counsel 2022;32:266–80.
22. Gillinder L, Britton JW. Seizures associated with autoimmune disorders - current treatment approaches. Semin Neurol 2025;45(2):275–86.
23. Burgess RC. Magnetoencephalography for localizing and characterizing the epileptic focus. Handb Clin Neurol 2019;160:203–14.
24. Kanner AM, Bicchi MM. Antiseizure medications for adults with epilepsy: a review. JAMA 2022;327(13):1269–81.
25. Stephen LJ, Harden C, Tomson T, et al. Management of epilepsy in women. Lancet Neurol 2019;18(5):481–91.
26. Omidi SJ, Lundstrom BN. Invasive neurostimulation for the treatment of epilepsy. Semin Neurol 2025;45(2):252–63.
27. Foster E, Carney P, Liew D, et al. First seizure presentations in adults: beyond assessment and treatment. J Neurol Neurosurg Psychiatry 2019;90(9):1039–45.
28. Musicco M, Beghi E, Solari A, et al. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. First seizure trial group (FIRST group). Neurology 1997;49(4):991–8.
29. Marson A, Jacoby A, Johnson A, Medical Research Council MESS Study Group. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet 2005;365(9476):2007–13.
30. Cavirani B, Spagnoli C, Caraffi SG, et al. Genetic epilepsies and developmental epileptic encephalopathies with early onset: a multicenter study. Int J Mol Sci 2024;19(25):1248.
31. Guerin J, Watson RE, Carr CM, et al. Autoimmune epilepsy: findings on MRI and FDG-PET. Br J Radiol 2019;92(1093). https://doi.org/10.1259/bjr.20170869.
32. Doppelbauer A, Zeitlhofer J, Zifko U, et al. Occurrence of epileptiform activity in the routine EEG of epileptic patients. Acta Neurol Scand 1993;87(5):345–52.
33. Baldin E, Hauser WA, Buchhalter JR, et al. Yield of epileptiform electroencephalogram abnormalities in incident unprovoked seizures: a population-based study. Epilepsia 2014;55(9):1389–98.
34. Faulkner HJ, Arima H, Mohamed A. Latency to first interictal epileptiform discharge in epilepsy with outpatient ambulatory EEG. Clin Neurophysiol 2012;123(9):1732–5.