Surgical Treatments, Devices, and Nonmedical Management of Epilepsy

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REVIEW ARTICLE

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ABSTRACT

OBJECTIVE: **Many patients with epilepsy are unable to achieve optimal seizure control with medical therapy. This article focuses on surgical approaches, dietary therapies, and seizure detection devices.**

LATEST DEVELOPMENTS: **For more than a century, resective epilepsy surgery has been a treatment option for some patients with drug-resistant epilepsy. Other surgical options have emerged for patients for whom resection is not possible or is associated with unacceptable risks, including minimally invasive epilepsy surgery and neurostimulation therapies. Dietary therapies, such as the ketogenic diet, can also help improve seizure control, especially in children. For patients with ongoing nocturnal convulsive seizures, seizure detection devices can alert caregivers and potentially reduce the risk of sudden unexpected death in epilepsy (SUDEP).**

ESSENTIAL POINTS: **Patients with drug-resistant epilepsy should be referred to comprehensive epilepsy centers to determine if they qualify for nonpharmacologic treatment options to reduce the risk of seizures and premature death and improve quality of life.**

INTRODUCTION

Although many people with epilepsy will become seizure free with antiseizure medication, about one-third of patients continue to have seizures despite the availability of many new antiseizure medications over the past 20 years.[1] Consequences of ongoing seizures include cognitive and neuropsychiatric decline, social and economic disruption, poor quality of life, risk of injury, and increased mortality.[2] In children, ongoing seizures can lead to neurodevelopmental delay or regression.[3] Therefore, it is essential to consider other treatment options for patients who are not responding to antiseizure medications, especially if they are having disabling seizures. Several surgical approaches to epilepsy treatment are available. Some patients with drug-resistant epilepsy may become seizure free with epilepsy surgery because their seizures arise from a single area of the brain that can be safely resected or ablated. Although some patients may not be candidates for a curative approach, palliative surgical procedures or neurostimulation devices can lead to a meaningful reduction in seizures and improved outcomes. Other

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nonpharmacologic treatments for seizures in patients with drug-resistant epilepsy include ketogenic diet therapies. Some people with epilepsy may continue to have seizures despite all available treatments. For these patients, devices can alert caregivers of convulsive seizures so they may provide aid in the peri-ictal period. This article discusses these interventions, examines their effectiveness, and provides guidance on identifying the best candidates for these approaches.

EPILEPSY SURGERY

Surgical treatment for epilepsy predates most antiseizure medications. The first modern surgeries for epilepsy were performed in the United Kingdom in the late 19th century. In the second half of the 20th century, the introduction of intracranial electrodes, long-term video-EEG telemetry, and advanced neuroimaging led to improvements in patient selection for resective epilepsy surgery and palliative procedures to reduce seizure frequency and severity. Despite advances, access to epilepsy surgery remained limited to patients treated at a handful of epilepsy centers. With increased training of specialists, stronger supportive evidence, safer diagnostic and therapeutic technologies, and the recognition that surgery is not a therapy of last resort, epilepsy surgery is more widely available.[4] In the United States, 256 centers offer some form of epilepsy surgery.[5]

Indications for Surgical Treatments

People with epilepsy typically must take antiseizure medications daily to maintain seizure control. Patients who fail to achieve seizure control with antiseizure medications due to lack of efficacy have drug-resistant epilepsy, which is defined by the International League Against Epilepsy as a "failure of adequate trials of two tolerated and appropriately chosen and used [antiseizure medication] schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[6] Estimates of the proportion of patients with drug-resistant epilepsy range from approximately 13% in community-based studies to approximately 37% in epilepsy clinic populations.[7] Although additional medication trials may lead to seizure remission in patients with drug-resistant epilepsy,[8] seizure freedom may not be durable, and side effects increase with additional antiseizure medications.

Surgical therapies for selected patients can improve seizure control, reduce seizure-related morbidity and mortality, reduce the burden of antiseizure medications, and improve quality of life.[9] These treatments have been traditionally divided into surgeries intended to cure through resection, disconnection, or ablation of the region of the brain responsible for seizure onset in focal epilepsy or to palliate, by reducing the frequency and severity of seizures through resection, ablation, disconnection or neurostimulation. Destructive surgeries to disrupt the site of seizure onset or prevent seizure spread are done through open surgery (CASE 7-1) or, in appropriate cases, laser interstitial thermal therapy. Minimally invasive destructive procedures are used less commonly to treat epilepsy and include stereotactic radiosurgery and radiofrequency thermal ablation.[10] Neurostimulation therapies include vagus nerve stimulation (VNS), thalamic deep brain stimulation (DBS), and responsive neurostimulation.[11]

The distinction between curative and palliative epilepsy surgery is not always clear. Many patients treated with resective surgery cannot discontinue all antiseizure medications, and surgery may be considered successful even if

CASE 7-1

A 33-year-old right-handed man presented to clinic for further evaluation of drug-resistant epilepsy since he was 12 years old. His seizures were characterized by a buzzing sound lasting 20 seconds that often progressed to difficulty speaking and understanding. He had tonic-clonic seizures from sleep 3 to 4 times per year. MRI and EEG findings are shown in FIGURE 7-1, demonstrating a probable left temporal focal cortical dysplasia and left centrotemporal spike-and-slow-wave discharges, respectively. He was taking lamotrigine and clobazam at the time of presentation. Treatment with levetiracetam, lacosamide, oxcarbazepine, zonisamide, and perampanel had failed because of a lack of efficacy. Because of the location of his cortical dysplasia near the eloquent language cortex, he underwent an awake craniotomy for intraoperative language mapping and an electrocorticography-guided resection of the lesion. He was seizure-free for more than 2 years after surgery but rare, focal impaired awareness seizures recurred after tapering clobazam. Clobazam was restarted and he continued to be seizure free at the last follow-up.

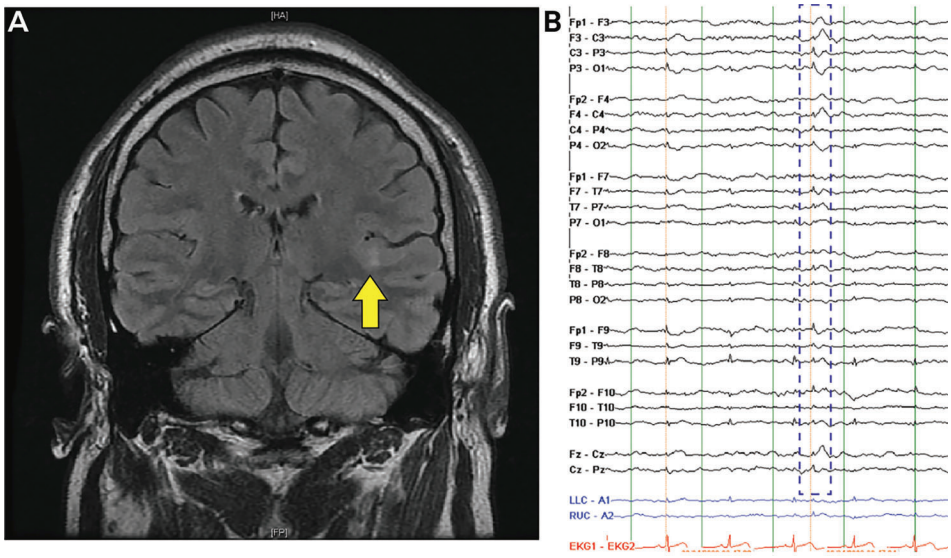

FIGURE 7-1

Imaging and EEG findings for the patient in CASE 7-1. *A*, Coronal fluid-attenuated inversion recovery (FLAIR) MRI showing cortical thickening and FLAIR hyperintensity consistent with focal cortical dysplasia type 2 in the left anterior transverse temporal gyrus (*arrow*). *B*, Interictal EEG showing left centrotemporal spike-and-slow-wave discharges.

COMMENT

This patient had drug-resistant focal epilepsy likely related to focal cortical dysplasia. He had focal to bilateral tonic-clonic seizures, which put him at high risk for sudden unexpected death in epilepsy (SUDEP). Normal intellect, a lesion on MRI, a single aura, and EEG concordant with the location of the lesion are good prognostic factors for seizure freedom with surgical resection.

nonmotor focal aware seizures (auras) persist.[12] Some patients with epilepsy that does not meet the definition for drug-resistant epilepsy may also undergo epilepsy surgery earlier in the course of their disease because the structural epileptogenic lesion (eg, cavernous malformation, low-grade glioma, focal cortical dysplasia) is located in noneloquent brain areas with low operative risk. These patients can have a better chance of a true cure and may be able to discontinue antiseizure medications. This approach may be particularly beneficial in children and people of childbearing potential, sparing them from potential neurodevelopmental and teratogenic effects of antiseizure medications, as illustrated in CASE 7-2.[13]

Identifying Candidates for Epilepsy Surgery

Many patients with drug-resistant epilepsy may be candidates for some type of epilepsy surgery. However, clinicians should assess the benefits and risks of surgical treatment and individualize based on patient preferences, the likelihood of benefit and harm from the procedure, and the dangers of ongoing seizures. As assessed by the American Academy of Neurology (AAN) epilepsy quality measures, all patients with drug-resistant epilepsy with disabling seizures should be referred to a comprehensive epilepsy center for consultation.[14] Evaluation at a comprehensive epilepsy center may include additional diagnostic testing to confirm the diagnosis of epilepsy and determine seizure type, both of which may

CASE 7-2

A 28-year-old right-handed woman presented to clinic for further management of her epilepsy. Two years before, she had a witnessed seizure with behavioral arrest, unresponsiveness, and lip-smacking. She denied prior auras or other events suspicious of unrecognized seizures. Her EEG showed right midtemporal spike-wave discharges, and her MRI demonstrated a small right temporal cavernous malformation. She was initially treated with levetiracetam but did not tolerate it because of mood side effects, so she switched to lamotrigine. She had several additional brief seizures but was seizure free since her dose was increased to 600 mg/d. She was interested in becoming pregnant soon and was concerned about the teratogenic and neurodevelopmental risks of her antiseizure medications. After discussion, she underwent electrocorticography-guided resection of the right temporal cavernoma and surrounding hemosiderin-stained brain tissue. She was seizure free postoperatively, and her EEG did not show any residual epileptiform activity. After 1 year, she was able to wean off lamotrigine. Two years later, she gave birth to a healthy baby girl.

COMMENT

This case illustrates a patient who may not have drug-resistant epilepsy and could pursue resective surgery. This patient had a superficial epileptogenic lesion in noneloquent cortex and could undergo a lesionectomy guided by intraoperative electrocorticography with a high chance (>75%) of being seizure free and no longer needing antiseizure medications.

lead to optimal medical treatment. Epilepsy centers can also assess patients for epilepsy surgery and other nonpharmacologic therapies and have expertise in performing surgical interventions and managing neurostimulation therapies. After careful assessment, some patients and caregivers may choose to continue antiseizure medication trials, but repeat evaluation should occur if patient and neurologist goals are not met. Patients treated at a comprehensive epilepsy center have reduced premature mortality compared with those treated in community practice, regardless of whether they have surgery.[15] FIGURE 7-2 shows a suggested algorithm for approaching a patient with drug-resistant epilepsy.

The International League Against Epilepsy recommends referral for surgical evaluation as soon as the patient is identified as having drug-resistant epilepsy, regardless of the epilepsy type. In addition, their guidelines also recommend

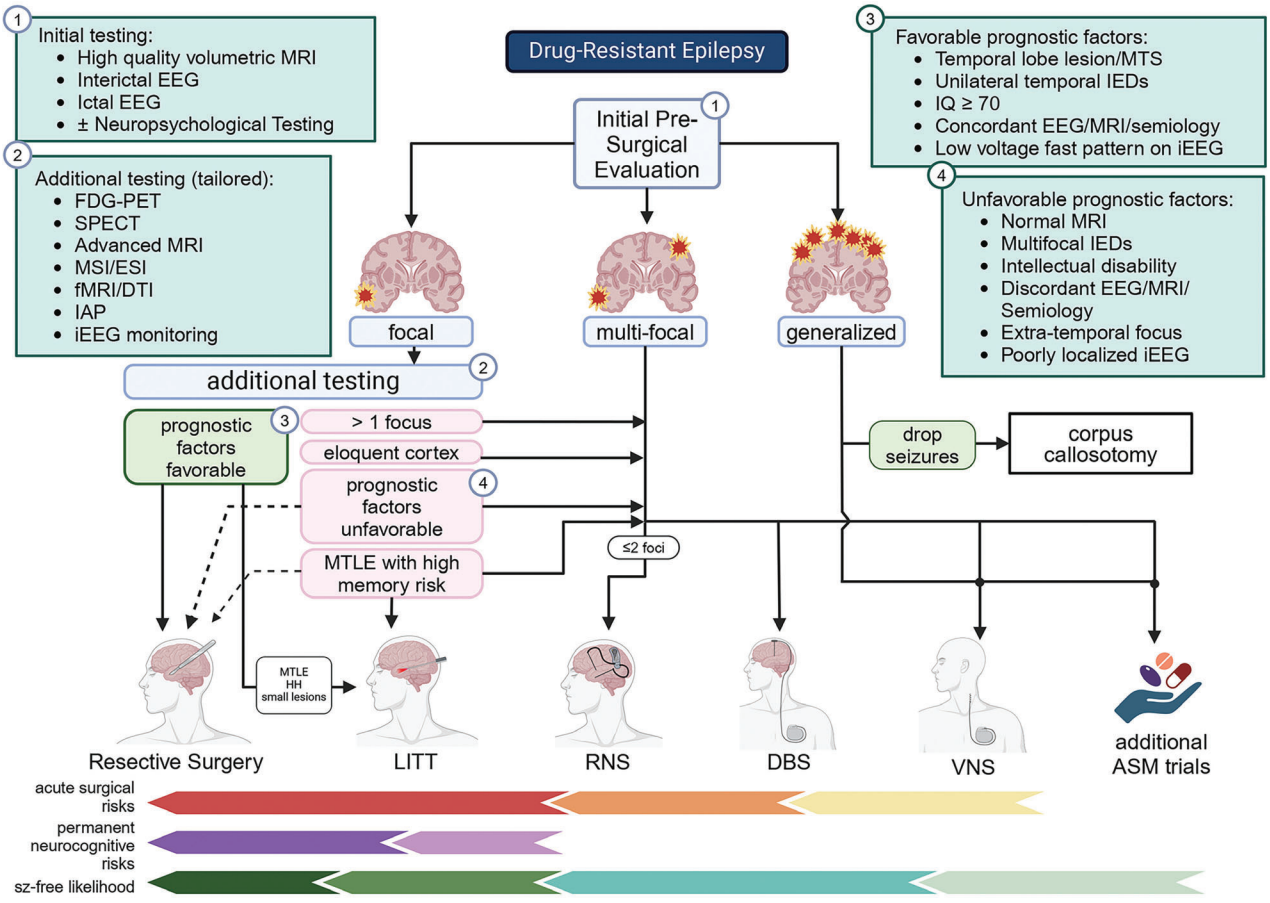

FIGURE 7-2

Surgical treatment algorithm for patients with drug-resistant epilepsy and the relative risks and benefits of each approach. Advanced MRI may include 7T MRI and MRI postprocessing techniques such as morphometric analysis. Figure created with BioRender.

ASM = antiseizure medication; DBS = deep brain stimulation; DTI = diffusion tensor imaging for tractography; ESI = electrical source imaging; FDG-PET = fludeoxyglucose positron emission tomography; fMRI = functional MRI; HH = hyperthalamic hamartoma; IAP = intracarotid amobarbital procedure (ie, the Wada test); IEDs = interictal epileptiform discharges; iEEG = intracranial EEG; IQ = intelligence quotient; LITT = laser interstitial thermal therapy; MSI = magnetic source imaging; MTLE = mesial temporal lobe epilepsy; MTS = mesial temporal sclerosis; RNS = responsive neurostimulation system; SPECT = single positron emission computed tomography; sz = seizure; VNS = vagus nerve stimulation.

surgical referral for patients with epileptogenic lesions in noneloquent cortex regardless of treatment response.[16] Despite these recommendations, many studies have noted significant delays from the onset of drug-resistant epilepsy to referral for surgical evaluation in children and adults.[16,17] Clinician barriers to timely referral include a failure to appreciate drug resistance; lack of knowledge regarding indications, benefits, and risks of epilepsy surgery; and underappreciation of the risks of ongoing seizures.[18] Systemic barriers, such as insurance coverage, cost, and geography also contribute to delayed referrals.[16] Several simple tools have been developed to assist neurologists in identifying patients who may benefit from resective surgery and should be referred for evaluation based on data available at the time of referral. An online tool (epilepsycases.com) is available to assist clinicians with determining both the appropriateness and priority of referrals using eight multiple-choice questions

TABLE 7-1A

Epilepsy Surgery Grading Scale[a,b]

	Score[c]
IQ < 70	-1
Unilateral focal motor activity	-3
MRI	
Normal	2
Unilateral mesial temporal sclerosis	5
Other temporal lesion	3
Extratemporal lesion	2
Two or more lesions	1
Interictal EEG	
No interictal epileptiform discharges	2
Unilateral temporal interictal epileptiform discharges	3
Unifocal extratemporal interictal epileptiform discharges	2
Bilateral independent or multifocal epileptiform discharges	2
Generalized or bisynchronous epileptiform discharges	1
Concordance of EEG and MRI findings	
Concordant	2
Partially concordant	1
Not concordant	0

[a] Modified from Hadady L, et al, Epilepsia.[23] © 2023 International League Against Epilepsy.
[b] This is a validated predictive tool for use at the time of presurgical referral to determine the likelihood of proceeding to epilepsy surgery and becoming free of disabling seizures at 2 years.
[c] A total score of 8 to 10 (grade I) indicates a high chance of seizure freedom (>70%) following surgery. A total score of 4 to 7 (grade II) indicates a moderate chance of seizure freedom (40% to 60%). A total score <4 indicates a low chance of seizure freedom (<40%).

about seizure type, severity, and frequency; epilepsy duration; antiseizure medication use, and MRI and EEG findings.[19,20] Several calculators using simple clinical and testing features available at the time of referral before presurgical evaluation have been developed to help clinicians determine the likelihood of seizure freedom with resective epilepsy surgery. These tools, including the Epilepsy Surgery Grading Scale[21] and the seizure freedom score,[22] have good predictive performance in identifying which patients with drug-resistant epilepsy are most likely to proceed to and benefit from resective epilepsy surgery to help prioritize referrals and have recently been validated in an independent cohort (TABLE 7-1A and TABLE 7-1B).[23] Validated tools for palliative surgeries are not yet available.

Benefits of Epilepsy Surgery

The best evidence for the benefits of epilepsy surgery exists for resective procedures. A 2015 systematic review[24] found that 64% of more than 16,000 surgically treated patients included in studies of epilepsy surgery achieved at least 1 year of freedom from disabling seizures. The pooled analysis of two randomized controlled trials comparing surgery with continued medical therapy (one in adults with temporal lobe epilepsy[25] and one in children with a broad range of epilepsies[26]) found that 70% of participants in the surgery group and 7% of participants in the medical therapy arm were free of disabling seizures at 1 year, a relative risk reduction of 9.8 (95% confidence interval [CI], 4.8 to 20.2). However, the durability of postoperative seizure freedom is variable. Greater than 5-year seizure freedom was maintained in 66% of patients who had undergone temporal lobe resections but only in 28% of patients who had undergone frontal lobe resections.[27] Even seizure-free outcomes following anterior temporal lobectomy may not be durable. Of patients who were seizure free 2 years after surgery, 22% to 37% experienced seizure recurrence in longer-term follow-ups (>10 years).[28,29] In children, long-term seizure outcomes are slightly better, with one estimate suggesting that 61.2% remained seizure free after 10 years.[30] When seizures recurred, they were typically less frequent or severe than before surgery.

Seizure Freedom Score[a,b] TABLE 7-1B

	Score[c]	
	Yes	No
Normal MRI	0	1
History of tonic-clonic seizures	0	1
More than 20 seizures per month	0	1
Epilepsy duration >5 years	0	1

[a] Modified from Hadady L, et al, Epilepsia.[23] © 2023 International League Against Epilepsy.
[b] This is a validated predictive tool for use at the time of presurgical referral to determine the likelihood of proceeding to epilepsy surgery and becoming free of disabling seizures at 2 years.
[c] A total score of 3 to 4 indicates a high chance of seizure freedom (>70%). A total score of 2 indicates a moderate chance of seizure freedom (40% to 69%). A total score of ≤1 indicates a low chance of seizure freedom (<40%).

Surgery can improve quality of life. A 2023 meta-analysis of 16 studies that included adults undergoing resection, ablation, or disconnection for drug-resistant epilepsy found that about half of patients experienced clinically significant improvements in quality of life.[31] This finding was partially correlated with freedom from disabling seizures after surgery and was also related to presurgical cognitive status, anxiety, and depressive symptoms, which negatively impact quality of life but may not be improved with epilepsy surgery.[31] A meta-analysis of 18 studies demonstrated that surgery for children with drug-resistant epilepsy also improves quality of life. Although quality of life improvement correlated with seizure control, preoperative cognitive status did not affect quality of life change as it did in adults.[32] In controlled trials, quality of life improved significantly in the surgical group but not in the continued medical therapy group in adults[25,33] and children.[26]

Epilepsy surgery is also associated with lower overall mortality and lower incidence of sudden unexpected death in epilepsy (SUDEP),[34,35] with the lowest risk among patients who became seizure free. This is expected because ongoing seizures, especially tonic-clonic seizures, are the most significant driver of SUDEP risk.[36] Some indirect evidence suggests that neuromodulation treatment such as VNS or responsive neurostimulation is associated with mortality and SUDEP rates lower than what are expected in patients with drug-resistant epilepsy.[34]

Epilepsy surgery and associated diagnostic testing are expensive. However, studies have suggested that, even when direct care costs such as hospitalizations, emergency department visits, and medications are considered, epilepsy surgery is cost-effective compared with continued antiseizure medication therapy alone. For temporal lobe surgery, modeling suggests that surgery becomes cost-effective after 4 years and after only 3 years if indirect costs of drug-resistant epilepsy, such as lost productivity of the patient and caregivers, are considered.[37] A 2022 meta-analysis suggested that epilepsy surgery was associated with a 20% gain in employment compared with the presurgical baseline.[38]

Risks of Epilepsy Surgery

Resective epilepsy surgery has short- and long-term risks. Minor neurologic complications are usually self-limited, treatable, or nondisabling and occur in 10% to 15% of patients.[39] The most common minor neurologic complications include quadrantanopia (18% of all temporal lobe resections), cranial neuropathies (2%), and transient language and motor dysfunction (3.7% and 3.1%, respectively).[39] Self-resolving or treatable complications, including CSF leak, aseptic meningitis, and intracranial hematoma, occur in 5.1% of patients.[39] The rate of major permanent neurologic deficits is 4.7%, and extratemporal and pediatric surgeries are associated with higher risk.[39] The most common major complications are hemianopia and weakness. Major medical complications occur in 1.5% of cases.[39] Serious infections and hydrocephalus requiring intervention are most common. Mortality associated with epilepsy surgery is very rare, occurring in less than 0.6% of cases.[39]

Approximately 30% to 40% of people with epilepsy evaluated for epilepsy surgery undergo invasive intracranial EEG monitoring to delineate the epileptogenic cortex to target for treatment and to determine if the area involved is eloquent.[40] Patients with extratemporal or nonlesional epilepsies are more likely to have invasive monitoring. In North America, intracranial EEG, with subdural or depth electrodes placed via a craniotomy, was commonly used until the past decade. Since then, less invasive, stereotactically placed depth

electrodes via small twist drill holes, used in many European centers, are more widely used and have been facilitated by the growing implementation of intraoperative robotics to improve the speed and accuracy of electrode placement. Stereoelectroencephalography is associated with fewer complications, decreased pain medication use, and similar seizure-free outcomes compared with craniotomy-based procedures.[41,42] The most common stereoelectroencephalography complications are intracerebral hemorrhage and infection at a rate of approximately 1% to 4%, and long-term deficits are rare.[42,43] This is comparatively a safer procedure with the rate of complications about 25% to 50% of those reported for subdural electrodes.

Resective epilepsy surgery may involve the removal of up to 15% of cortical volume, as in the case of temporal lobectomy. Although this cortex may not be functioning optimally because of the underlying dysfunction leading to epilepsy, epilepsy surgery may lead to deterioration in cognitive functions. Up to 44% of patients with left temporal resections and 20% with right temporal resections experience a verbal memory decline.[44] These changes often do not manifest as subjective memory symptoms. Left temporal resections are also associated with a 34% reduction in naming, whereas changes in overall cognitive function and executive function are uncommon, regardless of the side of surgery.[44] Cognitive decline after temporal lobectomy is associated with reduced postoperative quality of life.[45] Perhaps because of the deleterious effects of seizures and epileptiform discharges, some patients experience improvements in some cognitive domains, such as verbal fluency, after surgery.[44] Approximately one-third of children experience a decline in one or more cognitive domains after epilepsy surgery, although 10% to 30% show improvement.[46,47]

Minimally Invasive Epilepsy Surgery

Given the cognitive and surgical risks of epilepsy surgery, there has been an interest in less invasive procedures to treat the seizure focus. Several approaches have been examined, including selective amygdalohippocampectomy, stereotaxic radiosurgery, radiofrequency ablation, and laser interstitial thermal therapy. These techniques are typically used for mesial temporal lobe epilepsy but can be applied to treat other areas as well. Although the chance of postoperative seizure freedom is lower,[48,49] laser interstitial thermal therapy and radiofrequency ablation may also be associated with lower rates of surgical complications.[49] Although cognitive changes occur with all surgical approaches, laser interstitial thermal therapy may have lower risks of postoperative naming and verbal memory dysfunction than anterior temporal lobectomy.[50,51]

Laser interstitial thermal therapy has emerged as the dominant minimally invasive ablative treatment in North America. The procedure involves transmitting laser energy via a stereotactically placed fiber optic probe to thermocoagulate brain tissue. Real-time MRI measurement of tissue temperature is used to estimate and control the volume of tissue that is thermocoagulated. Although laser interstitial thermal therapy is most commonly used to treat mesial temporal lobe epilepsy with hippocampal sclerosis, it is also used for the treatment of epilepsies arising from deep lesions that are difficult to reach safely via open approaches such as hypothalamic hamartomas[52,53] and periventricular nodular heterotopias.[54,55] Laser interstitial thermal therapy is not without operative risk, and intracranial hemorrhage rates are approximately 1.5%. In studies of laser interstitial thermal therapy for mesial temporal lobe epilepsy,

KEY POINTS

- Patients have drug-resistant epilepsy when two or more appropriate antiseizure medications fail to control their seizures.
- Thirteen percent to 37% of people with epilepsy have drug-resistant epilepsy, and even those who have good seizure control may have intolerable medication side effects.
- Curative surgery aims to resect or ablate the seizure focus to make a patient seizure free.
- A lesional resection may not be feasible in some patients, but the surgical intervention can reduce the frequency and severity of seizures.
- Compared with continued medical therapy in patients with drug-resistant epilepsy, resective surgery offers a higher chance of seizure freedom and improved quality of life.
- Patients with drug-resistant epilepsy who have successful surgery have lower mortality rates.
- Surgery for drug-resistant epilepsy is cost-effective after 3 to 4 years.
- Resective epilepsy surgery carries risks, including neurologic complications and rare mortality.

common acute neurologic side effects included visual field defects (8.8%) and cranial neuropathies (3.1%), mostly transient third and fourth nerve palsies.[49] Serious, long-term complications after laser interstitial thermal therapy for hypothalamic hamartomas in experienced centers are also low compared with open or endoscopic procedures.[52,56]

Corpus Callosotomy and Other Disconnection Procedures

Disruption of some or all of the corpus callosum to prevent seizure spread or bilateral hemispheric expression of seizures has been used as a palliative procedure since the 1940s.[57] It is currently used to reduce the frequency of tonic and atonic seizures in patients with generalized and multifocal epilepsy because these seizure types have significant morbidity due to falls. A meta-analysis of 58 studies demonstrated that corpus callosotomy eliminated drop seizures, defined as any tonic or atonic seizure leading to falls, in 55% of patients; 19% of patients in the same analysis became seizure free entirely over the follow-up period.[58] Factors associated with the elimination of drop seizures included a history of infantile spasms, shorter epilepsy duration, lack of structural abnormalities on MRI, and disruption of the entire corpus callosum (complete callosotomy).[58] Complications occurred in 8% to 12% of surgeries. The most common neurologic complications are leg weakness, akinesia, and mutism, which are related to the surgical approach and are typically transient. The lasting consequences of callosal disconnection may include attention difficulty; deficits in naming, writing, reading; and coordination problems, especially involving bimanual tasks.[59] Risks of complications may be higher in complete callosal transection, and many centers favor disruption of the anterior two-thirds of the callosum, which may be safer but less effective.[58] Some centers use selective posterior callosal disruption, targeting fibers that connect the premotor and motor cortex for drop seizures. In a small series, these limited disconnections appeared effective with a low risk of language or motor complications.[60] Some centers have used laser interstitial thermal therapy for callosotomy, which may have less operative risk and shorter hospitalizations than open procedures.[61]

Children with severe and widespread regional or hemispheric epilepsies may undergo other disconnection procedures. Anatomic hemispherectomies were introduced in the 1930s and became an effective treatment for severe epilepsies restricted to one hemisphere but were associated with significant immediate and late complications. Over the years, the procedure evolved into functional hemispherectomy, in which the cortex is mainly preserved but the underlying white matter is disconnected, resulting in fewer complications.[62] Indications for hemispherectomy include lesions, which lead to widespread seizure-onset regions restricted to one hemisphere, such as perinatal stroke, Rasmussen encephalitis, large malformations of cortical development, and Sturge-Weber syndrome.[62,63] Hemispherectomy in children is associated with a 73% seizure-free rate at the last follow-up. Long-term neurologic complications of hemispherectomy include hemiparesis, hemianopsia, and language dysfunction.[64] The degree of language decline depends on the side of the operation and the etiology of epilepsy but not the age at surgery.[65] Although less common, hemispherectomy is also used in adults with similar seizure outcomes as children.[66,67] Given the expected neurologic risk, hemispherectomies are performed in patients who may already have some degree of hemiparesis and limited risk for significant postoperative language dysfunction. Other disconnection surgeries include posterior quadrant disconnection, in which the

parietal, occipital, and temporal cortices are disconnected, and sensory and motor cortices are spared.[68]

NEUROSTIMULATION

Electrical stimulation of the nervous system to treat epilepsy, targeting the anterior thalamus and cerebellum, was first explored more than 50 years ago.[69] Since then, three approaches have been approved for electrical stimulation of the central or peripheral nervous system to treat drug-resistant epilepsy. The appeal of neurostimulation treatments is that they do not include the risk of permanent neurologic deficits associated with resective surgeries, ablations, and disconnections, and do not have the central nervous system and systemic toxicities of antiseizure medications. However, the overall rates of seizure freedom with neurostimulation techniques are low, and these procedures are considered palliative. They can particularly benefit patients with generalized and multifocal epilepsies or those who are not able to undergo resection because of the overlap of their seizure-onset zone with eloquent cortex.

Vagus Nerve Stimulation

VNS was approved for the treatment of drug-resistant focal epilepsy in Europe in 1994 and in the United States in 1997. The VNS pulse generator is implanted under the skin of the left side of the chest, and a lead is attached to the left vagus nerve. Although older models stimulate the nerve in an open-loop fashion and provide the ability for on-demand stimulation by using a magnet, some newer models also offer the option of closed-loop stimulation by using heart rate elevation as a marker for seizure activity. The mechanisms of antiseizure action for VNS are not entirely clear despite more than 30 years of use. Evidence supports the effects on ascending noradrenergic, cholinergic, and γ-aminobutyric acid–mediated (GABA-ergic) projections through antidromic activation of the brainstem and effects on neuroinflammation.[11] A meta-analysis of 74 studies suggests that VNS reduces seizure frequency by 36% at 3 months and 51% after a year of treatment.[70] In a pooled analysis, only 2% to 5% of treated patients were seizure free after 4 months, and 0% to 8% became seizure free at long-term follow-up.[71] Although initial approval was for the treatment of focal epilepsy in adults, some evidence supports the use of VNS in children with generalized and focal seizures, as well as in patients with Lennox-Gastaut syndrome, and the most recent AAN guideline suggests it "may be considered" in these populations.[72] Predictors of response include generalized seizure types, onset in patients older than 12 years, and nonlesional MRI.[70,71] VNS treatment is also associated with improvements in quality-of-life and mood measures.[11] Adverse effects of VNS surgery occur in 9% of patients; infections, local hematomas, and vocal cord paralysis are the most common. Sixty-two percent of patients experience voice changes during stimulation, and a significant minority report cough or pain related to stimulation. Changing stimulation parameters can typically mitigate these side effects. VNS can also aggravate obstructive sleep apnea, and at-risk patients should be screened with polysomnography.[11]

Thalamic Deep Brain Stimulation

DBS targeting the anterior nucleus of the thalamus was approved for treating drug-resistant focal epilepsy in Europe in 2010 and the United States in 2018. Stimulation may control seizures by reducing the synchronization of epileptic

KEY POINTS

- **Minimally invasive epilepsy surgery such as laser interstitial thermal therapy has lower cognitive risks but is less likely to lead to seizure freedom. It is a treatment option for some forms of focal epilepsy.**
- **Neurostimulation techniques offer palliative treatment for drug-resistant epilepsy without resective surgery risks or antiseizure medication toxicities.**
- **Vagus nerve stimulation is the least invasive neurostimulation technique but may have lower efficacy than intracranial stimulation with deep brain stimulation and responsive neurostimulation.**

brain networks, but the exact mechanisms are elusive.[11,69] In a pivotal, controlled, blinded trial, median seizure reduction at 3 months was 40% in the treatment arm and 15% in the control group.[73] At 2 years, the median seizure reduction was 56%, and about half of the patients had a 50% or greater reduction in seizures.[73] Thirteen percent to 18% of patients had 6 months or more of seizure freedom in long-term follow-up, although fewer had sustained seizure freedom.[11] A recent prospective registry study found a more modest 33% reduction in seizures at 2 years, with only 3% patients seizure free.[74]

Adverse effects of anterior nucleus DBS include surgical complications, including infection in 9% and effects directly related to stimulation, including paresthesia (18%), worsening depressive symptoms (15%), and memory symptoms (13%).[11] Anterior nucleus DBS can disrupt sleep,[75] although this could be mitigated by changing stimulation parameters.[76] Predictors of response may include the position of the stimulating electrodes within the anterior nucleus. Patients with temporal lobe epilepsy may have better outcomes compared with patients with extratemporal epilepsy, although this was not statistically different in either the initial pivotal trial or subsequent prospective studies.[73,74] Other thalamic targets have been proposed for patients with generalized seizure types, including the centromedian thalamic nucleus.[69] Although preliminary studies of centromedian nucleus stimulation are promising for disorders such as Lennox-Gastaut syndrome,[77] more extensive controlled trials are needed.

Responsive Neurostimulation

The responsive neurostimulation is a closed-loop device placed in the skull that continuously senses the electrocorticogram from two intracranial electrodes with four contacts, each placed in the putative epileptic foci. It delivers electrical stimulation in response to abnormal activity patterns individualized to the patient's ictal onset pattern. Responsive neurostimulation was approved in 2013 in the United States to treat drug-resistant focal-onset seizures in adults with two or more seizure foci. Mechanisms of action include acute disruption of seizure onset with electrical stimulation and possible long-term neuromodulatory effects that reduce seizure initiation.[11] In a pivotal randomized controlled trial of responsive neurostimulation, the median seizure reduction at 3 months of treatment was 38% in the treatment group and 17% in the control (sham) group.[78] Open-label extension studies found 44%, 53%, and 66% reduction in seizures at 1, 2, and 6 years, respectively.[79] A minority of patients became seizure free for at least 3 months (9% at 2 years and 28% in 5- to 9-year follow-up), although durable seizure freedom was very rare.[79–81] Surgical complications include infections (3% at 3 months and up to 12% in long-term follow-up) and intracranial hemorrhage (3%). Treatment-related side effects include paresthesia, mood changes, and memory symptoms, although formal testing suggested no impact on memory or language function.[11] No clear predictors of response to treatment have emerged.

Of the approved neurostimulation devices, responsive neurostimulation is unique in its ability to record chronic ambulatory electrocorticography, which can provide an objective measure of seizure frequency under naturalistic circumstances. Among patients with bilateral mesial temporal lobe epilepsy, responsive neurostimulation recordings may identify a subset of patients with seizures arising predominantly or exclusively from one temporal lobe while on their antiseizure medications who subsequently can undergo curative or palliative mesial temporal resection, as illustrated in CASE 7-3.[82]

OTHER NONPHARMACOLOGIC THERAPIES

Not all patients may be good candidates for or willing to accept the risks of surgical intervention. Patients treated with neurostimulation are unlikely to achieve seizure freedom. Other interventions can help improve seizure control and quality of life in people with epilepsy.

Dietary Therapy

Although additional antiseizure medication trials may achieve acceptable seizure control, dietary therapy is another nonpharmacologic approach to treating patients with drug-resistant epilepsy. Specific diets include the classic ketogenic diet, medium-chain triglyceride ketogenic diet, modified Atkins diet, and low-glycemic-index treatment. The exact mechanisms of the ketogenic diet and modified Atkins diet are unknown, but preclinical studies implicate anti-inflammatory and neuromodulatory effects through changes in gene expression, brain metabolism, and gut microbiome.[83] A 2020 systematic review and meta-analysis[84] found that children with drug-resistant epilepsy who were treated with a ketogenic diet or modified Atkins diet had better response rates than those receiving usual care. Children had a nearly 6 times greater likelihood of achieving a 50% or greater reduction in seizures compared with usual care and, depending on the study, a 10% to 55% seizure freedom rate. Results on efficacy in adults are less conclusive and limited by small samples. Side effects in ketogenic diet–treated patients included vomiting, diarrhea, constipation, and weight loss. Other risks included hyperlipidemia, lethargy, and hypercalciuria. Gastrointestinal side effects and tolerability were less common in patients treated with the modified Atkins diet. A 2023 randomized trial in infants with drug-resistant epilepsy found no difference in seizure control compared with additional antiseizure medication trials and similar tolerability.[85] Because of the complexity of the diets and the need to monitor nutritional status and metabolic side effects, trained dietitians in collaboration with specialty centers should oversee treatment. Diet therapy may be a reasonable palliative option for patients who may not be good candidates for curative epilepsy surgery.[86]

Epilepsy Self-Management Tools

Managing a chronic disorder such as epilepsy requires support between clinician visits to increase key skills such as disease knowledge, medication taking, monitoring symptoms and side effects, safety, and addressing key comorbidities that affect quality of life. Self-management programs for adults with epilepsy have focused on education and skill building, and randomized trials have suggested improvements in quality of life in a 2019 systematic review.[87] Specific self-management tools have also been developed to address depressive[88] and cognitive[89] symptoms, common comorbidities in epilepsy that negatively affect quality of life. The US Centers for Disease Control and Prevention's Managing Epilepsy Well Network developed evidence-based self-management tools for epilepsy (managingepilepsywell.org). For a more detailed discussion of epilepsy and comorbidities, refer to the article "Epilepsy Comorbidities" by Mark R. Keezer, MD, PhD[90] in this issue of *Continuum*.

DEVICES FOR SEIZURE ALERTING

People with epilepsy who have ongoing seizures, especially tonic-clonic seizures, are at high risk for SUDEP.[36] Patients who have nocturnal tonic-clonic seizures

KEY POINTS

- Responsive neurostimulation can record chronic ambulatory intracranial EEG, which can help guide epilepsy treatment decisions such as future resections.
- Dietary therapy can reduce seizure frequency and improve quality of life for patients with drug-resistant epilepsy. The best evidence for efficacy is in children.
- Several interventions are available to improve self-management of epilepsy and its comorbidities, including depression and subjective cognitive symptoms.
- Wearable seizure alert devices can alert caregivers of tonic-clonic seizures. They may improve seizure safety and reduce the risk of sudden unexpected death in epilepsy (SUDEP).
- Current wearable devices for seizure detection and alerting require a nearby caregiver to respond to the alert and provide aid in the peri-ictal period.

and are unsupervised at night are at the highest risk.[36] The protective effect of nighttime supervision, defined as someone who can adequately provide aid during or immediately after a seizure, has led to an interest in devices for seizure detection and alerting (CASE 7-4). In a case series of SUDEP observed during epilepsy monitoring, all deaths occurred when patients were unattended, and the latency between the terminal seizure and cardiopulmonary arrest was as long as 13 minutes.[91] Observations in hospitalized patients suggest that the sooner a nurse arrives at the bedside from seizure onset, the less the degree of postictal hypoxemia and the shorter the postictal coma.[92]

Although EEG signals remain the gold standard tool for seizure detection, current EEG-based sensors are not practical for long-term home use. Most

CASE 7-3

A 25-year-old graduate student presented to clinic for evaluation for drug-resistant epilepsy since the age of 14 years due to viral encephalitis. She was still having three to four focal impaired aware seizures per month. She had right mesial temporal sclerosis seen on MRI and right greater than left mesial temporal hypometabolism on positron emission tomography (PET). Interictal EEG demonstrated right greater than left anterior temporal epileptiform discharges, and EEG monitoring recorded four right temporal–onset and one left temporal onset–seizure with medication reduction. Stereoelectroencephalography evaluation recorded 12 electroclinical seizures, nine from the right hippocampus and three from the left hippocampus, also after medication reduction. She underwent responsive neurostimulation implantation with depth electrodes placed in the hippocampus bilaterally. After 1 year, her seizures were occurring 1 to 2 times per month with shorter postictal recovery. A review of the electrocorticograms demonstrated that 90% of her seizures started in the right hippocampal electrode (FIGURE 7-3). Based on these data, she underwent a palliative right anterior temporal lobe resection with amygdalohippocampectomy. The responsive neurostimulation remained to treat the left-onset seizures. After the surgery, she became free of disabling seizures and experienced brief auras only.

COMMENT

In this case, the patient demonstrated bilateral mesial temporal lobe epilepsy. She was not a candidate for curative resection or ablation because she had two independent seizure foci. Any form of neurostimulation was a reasonable palliative treatment option for her drug-resistant epilepsy, but responsive neurostimulation was chosen because of the ability to quantify seizures through chronic electrocorticography under naturalistic circumstances while she was taking antiseizure medications. After a year, it became apparent that most of her seizures that were not responding to treatment arose from the right hippocampus, and she was able to have a second palliative procedure, a resection, to treat these seizures.

marketed detection devices use peripheral sensors to detect seizure-related convulsive movements. The earliest devices for seizure alerting were sensors placed under the mattress to detect the rhythmic movements of tonic-clonic seizures. These devices, which use microphones or piezoelectric sensors, demonstrated a wide range of sensitivity (11% to 89%) compared with video-EEG monitoring in children and adults.[93] Video-based movement-detection devices have also been developed for nighttime motor seizure detection. Although one non–FDA-approved device is commercially available in the United States, limited data exist regarding its performance.[93]

Unlike mattress- and video-based seizure detection devices, wearable devices are not limited to use in a particular location. Early wrist-worn devices used

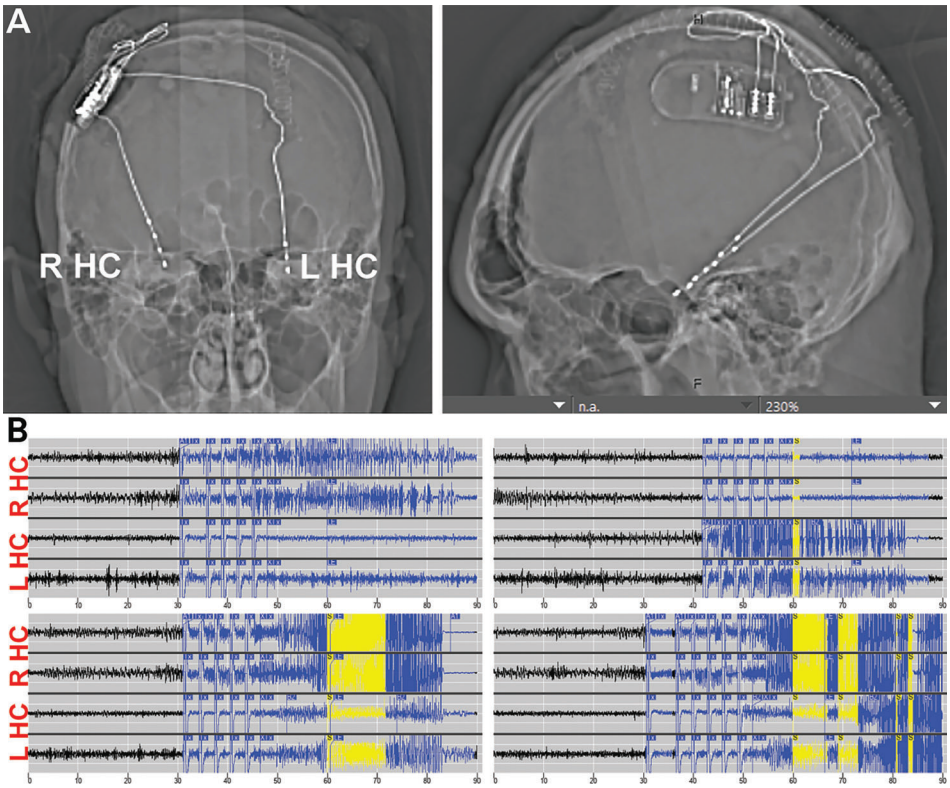

FIGURE 7-3

Responsive neurostimulator data for the patient in CASE 7-3. *A*, Coronal (*left*) and sagittal (*right*) CT scout image showing a responsive neurostimulation device in place with depth electrodes for sensing and stimulation placed in the hippocampus bilaterally. *B*, Examples of electrocorticograms recorded by the responsive neurostimulation for four consecutive seizures. In each plot, the top two traces are from the right hippocampal (R HC) contacts and the bottom two are from the left hippocampal contacts (L HC). The seizure in the *top right* electrocorticogram starts from the left whereas the remaining seizures start on the right.

multiaxis accelerometers and simple threshold algorithms to detect seizure-related motion. Although they are sensitive to tonic-clonic seizures, these devices demonstrated high false-alarm rates.[94] Subsequent devices added sensors, including photoplethysmography, to capture heart rate and electrodes to record electrodermal activity (a measure of sympathetic nervous system activity) and used machine-learning algorithms to improve specificity and potentially detect other motor seizures beyond tonic-clonic seizures. Some of these devices are purpose-built for seizure detection, whereas others are custom applications running on consumer smartwatches that use these sensors for fitness or health tracking. Other devices have used surface EMG sensors to detect seizure-related muscle contraction. Guidelines from the International League Against Epilepsy suggest that wearable devices accurately detect tonic-clonic seizures and can be used as adjuncts for seizure monitoring.[95] Only two wearable devices have been FDA approved for seizure detection and alerting during periods of rest. These are

CASE 7-4

An 18-year-old college student presented to the office for evaluation after a tonic-clonic seizure witnessed from sleep. He had his own bedroom in the dorm, but his suitemate heard a noise and entered to find him convulsing on the floor. On further questioning, he reported two additional episodes over the past year when he awoke from sleep, slightly confused, tired, and having bitten his tongue, for which he did not seek medical attention. His MRI was normal; an overnight EEG showed intermittent slowing over the right hemisphere. Lacosamide 150 mg 2 times daily was prescribed for seizure prophylaxis. His parents read about sudden unexpected death in epilepsy (SUDEP) and other risks of seizures and were wondering what additional steps they could take to keep him safe. The patient discussed his epilepsy and seizure first aid with his suitemate who agreed to sleep with the door between their rooms open at night so that he could better hear and respond to any seizure activity. The patient was prescribed a seizure-detection watch, which he used at night, but after 6 months without any further seizures, he stopped wearing it. The patient had a seizure 1 year later after forgetting his medications for 2 days while he was on vacation. He began using alarms on his phone to remind him to take his medications with good subsequent seizure control.

COMMENT

This patient had three unprovoked nocturnal tonic-clonic seizures and likely focal epilepsy. It is not certain that this antiseizure medication and this dose would be sufficient to control his seizures. Nocturnal tonic-clonic seizures put him at high risk for SUDEP. In addition to a discussion of medication adherence, limiting alcohol use, driving restrictions, and other safety measures, a seizure-detection device to wear at night, at least until treatment response is established, could be considered to mitigate his SUDEP risk. However, he would need to identify someone who could respond to a device alert quickly, such as a suitemate, and disclose his epilepsy as well as discuss basic seizure first aid.

a surface EMG sensor placed on the bicep and a wrist-worn device that uses accelerometry and electrodermal activity.[93] Only the latter is available (via prescription) in the United States. Some caregivers of children with epilepsy use simple baby monitors to detect the vocalizations and other sounds associated with seizures. Types of detection and alerting devices and use cases are summarized in TABLE 7-2.[96]

Current seizure detection devices have several limitations. One is that they are unable to detect seizures with little or no motor manifestations, such as many types of focal impaired-awareness seizures or absence seizures. Although these seizure types are low risk for SUDEP, they are often unrecognized, making quantification of an objective response to therapy difficult.[97] Furthermore, no trials have demonstrated that these alerting devices prevent SUDEP or injuries.[95] A significant limitation is that there needs to be a caregiver who can receive the alert and be able to provide timely peri-ictal intervention. There have been reports of seizure detection devices alerting caregivers who were not nearby, and the patient had died by the time help arrived.[98] Future devices may include wearable or minimally invasive limited EEG sensors that can detect seizures regardless of motor signs[99] and closed-loop devices that may be suitable for patients living alone.

HEALTH DISPARITIES

The care of people with epilepsy, especially those with drug-resistant epilepsy, is resource intensive and significantly affected by systemic and individual social

Seizure Detection Device Types and Related Performance for Different Seizure Types and Limitations TABLE 7-2

	Effective detection		Location			
Device type	Tonic-clonic seizure	Other	Mobile	Fixed or during sleep only	Remote caregiver alerting	Notes
Multimodal wearables	Yes	Sometimes[a]	Yes	Yes	Yes	High false-alarm rates during wakefulness, need to wear or charge device
Muscle activity sensors	Yes	No or unknown	No or unknown	Yes	Yes	High false-alarm rates during wakefulness, need to position correctly
Video devices	Yes[b]	Sometimes	No or unknown	Yes	Yes	Blankets and stuffed animals may interfere, limited to where camera is pointing
Mattress sensors	Yes	No or unknown	No or unknown	Yes	No or unknown	Limited to bed; sensitivity may be low for younger, lighter children
Audio monitor	Sometimes	Sometimes	No or unknown	Yes	No or unknown	No alarm system

[a] Some wearable devices can also detect other seizure types with major motor manifestations such as hypermotor and tonic seizures during sleep.[96]
[b] Performance data for video-based commercial detection devices are not available.

determinants of health.[100] Black adult and Black and Hispanic pediatric patients and patients with public insurance are less likely than White patients to undergo surgical treatment for their epilepsy.[101,102] In addition, geographic barriers limit access to comprehensive epilepsy centers, which may offer surgical treatments and diet therapy. Epilepsy centers are not distributed equitably across the country, and rural and indigenous populations are the least likely to have access to specialty care.[103] Some of the nonpharmacologic and nonsurgical options for epilepsy care reviewed in this article are costly and seldom covered by medical insurance. For instance, special diets often mean additional costs to prepare ketogenic diet–appropriate meals. Seizure detection devices are often not covered by medical insurance and have upfront and continuing costs for subscriptions. Outside the United States and especially in low- and middle-income countries, access to epilepsy specialty care and surgical treatments for drug-resistant epilepsy is limited.[104]

CONCLUSION

Although most people with epilepsy respond to antiseizure medications, one-third will continue to have seizures or experience intolerable side effects of treatment. Neurologists should refer these patients to a comprehensive epilepsy center to determine if they are candidates for surgical treatments for epilepsy or other nonpharmacologic treatments. Resective surgery, when feasible, can eliminate seizures in more than half of carefully selected patients, making it a valuable disease-modifying therapy for patients with epilepsy. However, surgery is often underutilized and plagued by delays in referral, especially among patients who live far from a comprehensive epilepsy center, are Black or Hispanic, or have public insurance. Less invasive surgical options, such as VNS, DBS, and responsive neurostimulation, can significantly reduce seizures when resection is not possible or has unacceptable risks. Dietary therapies may also help improve seizure control and quality of life, especially in children. Patients with ongoing nocturnal convulsive seizures are at high risk for SUDEP. Seizure-detection devices that alert caregivers may reduce this risk. More timely referrals to comprehensive epilepsy centers can help expand access to these potentially life-saving alternatives.

USEFUL WEBSITES

Epilepsy Surgery Evaluation
This online tool assists clinicians with determining both the appropriateness and priority of surgery referrals for patients with epilepsy.
epilepsycases.com

Managing Epilepsy Well Network
This website provides evidence-based self-management tools for patients with epilepsy.
managingepilepsywell.org

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