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Review of Epilepsy - Etiology, Diagnostic Evaluation and Treatment

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Abstract

Epilepsy is the fourth most common neurological disorder in the US, affecting nearly 2.5 million Americans. The economic impact of epilepsy represents estimated direct and indirect costs of 12.5 billion dollars per year. Patients with this disorder experience increased morbidity and mortality with long term fatality rates of 24%. Multiple diagnostic tools are used to identify and classify the seizure type/syndrome, etiology and localization of seizures, including electroencephalogram (EEG), magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT), magneto encephalogram (MEG), and neuropsychiatric testing. Despite 29 different antiepileptic medications that are available in the US, one third of patients remain refractory to pharmacological treatment. In these intractable epilepsy patients, non-pharmacological treatments can be considered. Commonly used non-pharmacological treatment options for epilepsy include epilepsy surgery, neurostimulation therapy, and diet therapy.

Keywords: Epilepsy; Seizure

Introduction

A seizure is a clinical manifestation, resulting from a brief episode of abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a braindisorder characterized by a chronic predisposition to generate epileptic seizures with secondary neurobiologic, cognitive, psychological, and social consequences. By definition, epilepsy requires typically two unprovoked seizures, separated by greater than 24 hours [1]. Epilepsy and seizures affect nearly 2.5 million Americans of all ages. Overall, epilepsy affects 1-3% of the US population. The incidence rate is U-shaped: the highest incidence rates are noted in young patients in neonatal and as well as in elderly patients over 75 years old [2,3]. Estimated direct and indirect costs from epilepsy and seizures are 12.5 billion dollars/year in the US, and there are approximately 200,000 new cases of epilepsy diagnosed every year [4,5]. This paper aims to introduce the current knowledge and understanding of epilepsy in various aspects of epidemiology, etiology, diagnostic work ups and treatment options to rehabilitation specialists without neurology background.

Patients with epilepsy are at an increased risk of premature death with a mortality risk of 1.2-9.3 of all causes of death and a 24% long term fatality rate [6,7]. Sudden unexpected death in epilepsy (SUDEP) is awell-known condition of sudden unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in a patient with epilepsy, with or without evidence for a seizure and excluding convulsive status epilepticus in which post-mortem examination does not reveal a toxicological or anatomical cause for death. The risk of SUDEP ranges from 1 to 9 per1000 epilepsy patients per year. The40 year cumulative risk increases up to 7% for all epilepsy patients and 12% in poorly controlled epilepsy [6,7].

There are various treatment options for epilepsy, with antiepileptic medications being the first line treatment. Despite29 different anti-epileptic medications being available in the US (Table 1), one third of patients still experience intractable seizures [8]. Medically intractable or refractory epilepsy is defined as the failure of adequate trials of two tolerated and appropriately chosen antiepileptic medication schedules with adequate doses [9]. Patients with intractable epilepsy experience a significantly increased risk of injuries and premature death, as well as negative consequences upon their quality of life, cognition, and mood [4,5,10-19]. Patients with epilepsy suffer from lower socioeconomic status and lower quality of life compared to other general population in validated quality of life in epilepsy questionnaire (QOLIE). Fewer epilepsy patients married or had children, higher education or achievement in later life than the general population [4,5,10,14,15]. Also, patients with poorly controlled epilepsy experience decline in memory and cognition [10,12,14,15,17]. Co-morbid mood disorders such as depression and anxiety are common and more prevalent in patients with epilepsy compared to the general population [15,19]. In these uncontrolled patients, other treatment options are available and dependentupon the seizure type, localization of seizure onset, age, and co-morbid conditions. These treatment options include epilepsy surgery, neurostimulation therapy, and diet therapy.

Result and Discussion

Seizure type and classification

In 1981, theInternational League against Epilepsy (ILAE) recommended an updated and consistent classification of seizures. In 2010, the ILAE-revised the terminology and concepts for organization of seizures and epilepsy were introduced, and included many epilepsy syndromes and pathophysiologic etiologies. The classifications are shown in Figure 4 [20].

Seizures can be provoked by a variety of influences including severe metabolic disturbance, head trauma, alcohol intake and withdrawal, fever, illness and some medications. Causes of epilepsy are also broad, and include traumatic brain injury, stroke, tumor, central nervous system (CNS) infection such as viral and bacterial meningoencephalitis, inflammation or autoimmune diseases, genetic causes such as SCN1A mutation in Dravet syndrome, and structural brain abnormalities including hippocampal sclerosis, cortical dysplasia and vascular malformation.

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	Syndrome	Genes and loci
Common Genetic Epilepsies	Febrile Seizures	8q13-q21 (FEB1), 19p (FEB2), 2q23-q24(FEB3), 5q15-q15(FEB4), 6q22-q24(FEB5), 18p11(FEB6)
	Genetic epilepsy with febrile seizures plus	SCN1A, SCN2A, SCN1B, GABRD, GABRG2, PCDH19
	Severe myoclonic epilepsy of infancy and related syndromes	SCN1A, SCN2A, GABRG2
	West syndrome and early infantile epileptic encephalopathy with suppression-burst	ARX, CDK15, STXBP1
	Malignant migrating partial seizures of infancy	KCNT1
	Other early onset epilepeis	PLCB1, PCDH19, KCTD7, BCKDK, SYN1, GRIN2B, GRIN2A, TNK2, KCNQ2
	Benign familial neonatal convulsions	KCNQ2, KCNQ3
	Benign familial neonatal-infantile seizures	SCN2A
	Benign familial infantile seizures	PRRT2, ATP1A2
	Familial infantile myoclonic epilepsy	TBC1D24
	Juvenile myoclonic epilepsy	EFHC1, GABRA1
	Childhood absence epilepsy	GABRG2, GABRA1, SLC2A1
	Epilepsy + paroxysmal exercise-induced dyskinesia	SLC2A1
	Autosomal dominant nocturnal frontal lobe epilepsy	CHRNA4, CHRNA2, CHRNB2, KCNT1
	Familial lateral temporal lobe epilepsy	LGI1
	Familial focal epilepsy with variable foci	DEPDC5
Common Autoimmune Epilepsies	Anti-NMDA antibody, Anti-GABAB antibody, Anti-AMPA antibody, Anti-LGI1 antibody, Anti-CASPR2 antibody, Anti-contactin-2 antibody, Anti-GAD antibody, Anti-VGKC antibody	

Table 1: Common Genetic and Autoimmune Epilepsies [19-25]

Diagnostic Work-Ups for Seizure and Epilepsy

It is important to find possible causes of seizures so that proper treatment can be administered. When a patient presents to a neurologist for seizures or epilepsy, adetailed history and neurological examination are undertaken to determinethe seizure etiology, type and localization of epilepsy foci to provide prognostic information. Routine laboratory tests in patients with new onset seizures include CBC, electrolytes, hepatic enzyme panel and toxicology screens to assess for potentially reversible causes [21]. Additionally, if bacterial, fungal, or viral infection orother inflammatory brain disorderis suspected, a lumbar puncture is performed for cerebral spinal fluid (CSF) analysis. In selected cases, further laboratory evaluationwith genetic, autoimmune and paraneoplastic panels, may provide additional information about the cause of seizures and epilepsy. Genetic and autoimmune epilepsy are relatively new diagnoses and have provided additional information about the etiology of epilepsy and epileptogenesis [22-28]. Figure 4 summarizes common genetic and autoimmune epilepsies.

Various diagnostic tools are utilized to identify and classify the seizure type/syndrome and etiology, including electroencephalogram (EEG), magnetic resonance imaging (MRI), and positron emission tomography (PET), single photon emission computed tomography (SPECT), magneto encephalogram (MEG), and neuropsychiatric testing. EEG plays a critical diagnostic role via sampling of electrical brain activity. Epileptiform discharges in EEG are highly correlated with epilepsy, but are not pathognomic. EEG confirmation of seizures can be made only when a seizure is captured during an EEG. The sensitivity of EEG for epilepsy is 50% and specificity is 98-99%, while serial EEGs can increase the sensitivity up to 80-90%. In addition, various activation procedures such as hyperventilation, photic stimulation and sleep deprivation can increase the sensitivity of the test [21]. Long term video-EEG monitoring has further provided improved diagnostic yield in seizures and epilepsy, and has been commonly used for seizure/spell characterization, rapid antiepileptic medication adjustment, and epilepsy surgery evaluation. The international 10-20 system is a standardized and widely used method to place scalp electrodes. Normal awake EEG is shown in Figure 1. A right temporal lobe seizure is shown in Figure 2.

Neuroimaging studies play an integral part of seizure and epilepsy evaluation for the determination of the structural and functional etiology of seizures. Current standard neuro-radiological imaging includes 3T brain MRI with coronal or oblique-coronal images using T1-weighted and T2-weighted sequences as well as fluid-attenuated inversion-recovery (FLAIR). Although 1.5T brain MRI can also localize seizure foci, it is less sensitive than higher field 3T MRI [29]. The sensitivity of MRI for intractable epilepsy is in general 82-86% [30,31]. Since many different lesions may cause seizures, MRI is often a starting point for differentiation. These lesions include mesial temporal sclerosis (MTS), congenital brain abnormalities both migrational and syndromic like Sturge Weber, tumors, infections and vascular malformations such as cavernous malformations and arteriovenous malformations. A classic case of MTS will exhibit hippocampal atrophy with abnormal T2 and FLAIR signal in the hippocampus (Figures 3a and 3b), as well as decreased FDG uptake in PET scan (Figure 3c).

In selected patients other imaging techniques are used including functional neuro-imaging. PET (Figure 3c) is used to demonstrate regional differences in metabolic activity, SPECT is used to analyze

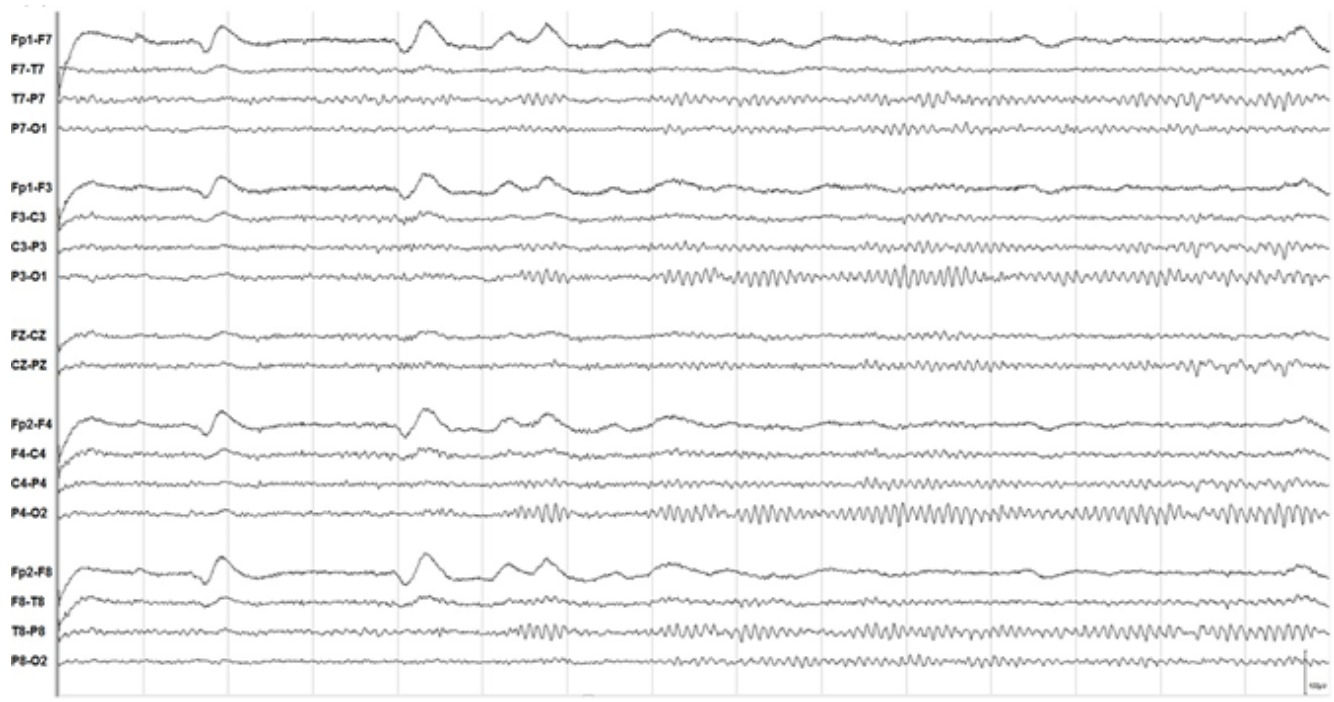

Figure 1: Electroencephalogram (EEG) of normal awake state. EEG setting: Bipolar montage, 15 sec/page, LFF 1Hz, HFF 70 Hz

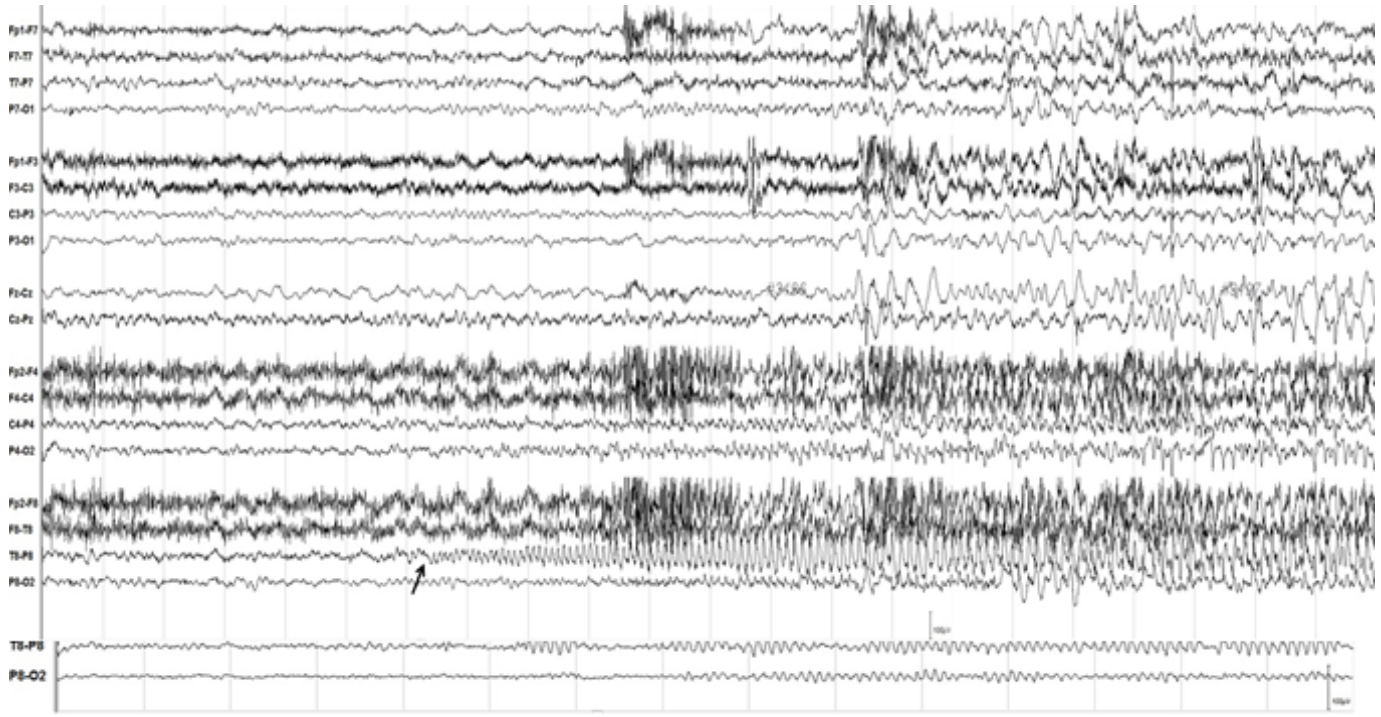

Figure 2: Electroencephalogram (EEG) of a right temporal lobe seizure. The arrow indicates the seizure onset with rhythmic alpha activity. EEG setting: Bipolar montage, 22 sec/page, LFF 1Hz, HFF 70 Hz

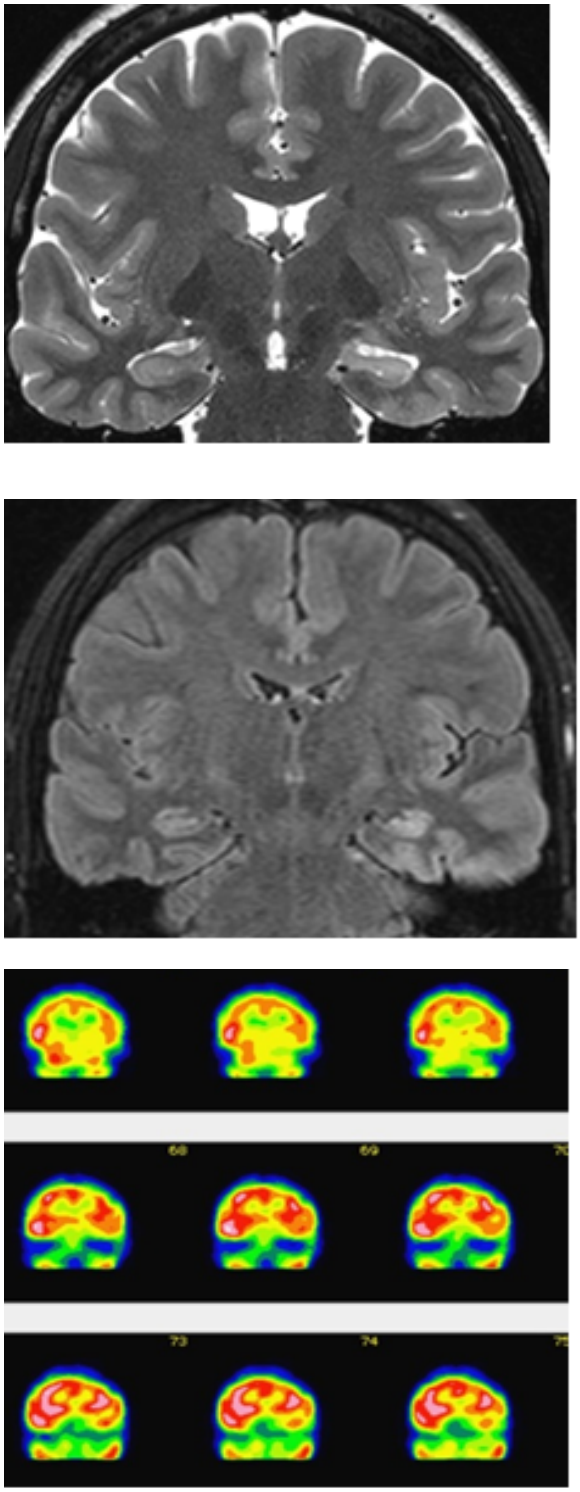

Figure 3: Mesial Temporal Sclerosis in MRI (A-B) and PET (C) Studies: The image on the left (A) is a coronal T2-weighted MRI exhibiting a smaller and slightly bright left hippocampus, while the figure on the right (B) is a coronal FLAIR image that better demonstrates the signal abnormality in the left hippocampus as well as the cortical/grey-white matter junction blurring in the adjacent temporal lobe cortex in this MTS patient. The image on the bottom (C) is the associated PET which shows decreased uptake in the inter-ictal phase in the left temporal lobe. This signifies focally-decreased metabolic activity, a classic finding in MTS.

regional differences in blood flow during a seizure (ictal SPECT) and between seizures (interictal SPECT) and MR Spectroscopy (MRS)is used to analyze the biochemical makeup of the imaged tissue [32-38]. MRS can be used to analyze a lesion to distinguish between tumor and gliosis. MEG and functional MRI have also been found to provide further information to localize a potential epileptogenic lesion and to identify the surrounding areas of eloquent cortex [39]. These studies are of particular assistance with cases in which focal seizures are suspected, but the brain MRI is negative.

Treatment Options

Pharmacological treatment

The primary treatment strategy for provoked seizures is the elimination of the underlying cause, such as correcting a metabolic disturbance, treating an underlying infection, etc [21]. Epilepsy is defined by two unprovoked seizures greater than 24 hours apart, and typically requires pharmacological treatment to prevent further seizures. Since the first anticonvulsant bromide was used in 1857, numerous antiepileptic medications have been developed and administered. Currently, there are 29 different antiepileptic medications available in the US (Table 2). Some of these medications including benzodiazepines, lamotrigine, levetiracetam, topiramate, valproic acid and zonisamide have broad spectrum coverage to treat both primary generalized and focal onset seizures, while others work better on focal onset seizures such as carbamazepine and oxcarbazepine. Only few medications have level A evidence in various types of epilepsy and epilepsy syndrome while most of medications have lower level evidence. The recent review of antiepileptic drug efficacy and effectiveness as initial monotherapy, conducted by international league against epilepsy showed level A evidence in levetiracetam, zonisamide, carbamazepine and phenytoin in adult patients with partial onset seizures while only oxcarbazepine is shown to have level A evidence in children with partial onset seizures. Valproic acid and ethosuximide have also level A efficacy and effectiveness in children with absence seizures. Other types of primary generalized epilepsy do not have clear level A evidence although there are multiple medications with level C and D evidence [40].

When neurologists choose medications to treat seizures, they consider the evidence of effectiveness/ efficacy, seizure classification, potential side effects, comorbid conditions, age and gender in order to select an effective medication while minimizing side effects [21,40,41]. Vaproic acid has been shown to significantly increase the risk of major fetal malformation in women with childbearing age whereas lamotrigine and levetiracetam are found to more safe choices. Chronic usage of antiepileptic medications can cause bone weakness. Certain hepatic enzyme inducing medications tend to have more drug-drug interactions and potentially become problematic in other co-morbid conditions, requiring anticoagulation, anti-tumoral or anti-HIV treatment. Some of antiepileptic drugs can affect the mood. Levetiracetam has higher risk of causing some irritability, depression and other mood disturbance whereas lamotrigine and valproic acid may have mood stabilizing effects. Certain medications such as topiramate and valproic acid are found to be useful to treat migraine headache [21,40,41].

Despite 29 different antiepileptic medications, one third of patients with epilepsy still suffer from medically refractory seizures [8]. Mohanraj and Brodie reviewed retrospective data of adolescent and adult patients' responses to sequential antiepileptic medication treatment in Scotland. Overall response rates with the first, second and third treatment schedules were 50.4, 10.7 and 2.7%, respectively, with

Acetazolamide	Eslicarbazepine	Lacosamide	Phenobarbital	Tiagabine
Carbamazepine	Ethosuximide	Lamotrigine	Phenytoin	Topiramate
Clobazam	Ezogabine	Levetiracetam	Pregabalin	Valproic Acid
Clonazepam	Felbamate	Lorazpeam	Primidine	Vigabatrin
Clorazepate	Fosphenytoin	Oxcarbazepine	Retigabine	Zonisamide
Diazepam	Gabapentin	Perampanel	Rufinamide	

Table 2: Available Medications Used in the Treatment of Epilepsy in US

(A)

ILAE Classification of Seizures

- **Generalized seizures**
  - **Tonic-clonic (in any combination)**
  - **Absence**
    - **Typical**
    - **Atypical**
    - **Absence with special features**
      - **Myoclonic absence**
      - **Eyelid myoclonia**
  - **Myoclonic**
    - **Myoclonic**
    - **Myoclonic atonic**
    - **Myoclonic tonic**
  - **Clonic**
  - **Tonic**
  - **Atonic**
- **Focal Seizures**
- **Unknown**
  - **Epileptic Spasm**

(B)

New ILAE Recommendation	
Descriptors of focal seizures according to degree of impairment during seizure	Without impairment of consciousness or awareness With observable motor or autonomic components Involving subjective sensory or psychic phenomena only With impairment of consciousness or awareness Evolving into a bilateral, convulsive seizure
Electroclinical syndromes and other epilepsies	Electroclinical syndromes arranged by age at onset Neonatal period Benign familial neonatal epilepsy Early myoclonic encephalopathy Ohtahara syndrome Infancy Epilepsy of infancy with migrating focal seizures West Syndrome Myoclonic epilepsy in infancy Benign infantile epilepsy Benign familial infantile epilepsy Dravet syndrome Myoclonic encephalopathy in nonprogressive disorder Childhood Febrile seizures plus Panayiotopoulos syndrome Epilepsy with myoclonic atonic seizures Benign epilepsy with centrotemporal spikes Autosomal-dominant nocturnal frontal lobe epilepsy Late onset childhood occipital epilepsy Epilepsy with myoclonic absences Lennox-Gastaut syndrome Epileptic encephalopathy with continuous spike-and-wave during sleep Landau-Kleffner syndrome Childhood absence epilepsy Adolescent-Adult Juvenile absence epilepsy Juvenile myoclonic epilepsy Epilepsy with generalized tonic-clonic seizures alone Progressive myoclonus epilepsies Autosomal dominant epilepsy with auditory features Other familial temporal lobe epilepsies Less specific age relationship Familial focal epilepsy with variable foci Reflex epilepsies Distinctive constellations Mesial temporal lobe epilepsy with hippocampal sclerosis Rasmussen syndrome Gelastic seizures with hypothalamic hamartoma Hemiconvulsion-hemiplegia-epilepsy Epilepsies that do that fit into any of these diagnostic categories can be distinguished first on the basis of presence or absence of known cause and then on the basis of the primary mode of seizure onset Epilepsies attributed to and organized by structural-metabolic causes Malformations of cortical development Neurocutaneous syndromes Tumor Infection Trauma Angioma Perinatal Insults Stroke Etc. Epilepsies of unknown cause Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se Benign neonatal seizures Febrile seizures

Figure 4: ILAE Classification of Seizures (A) and New Recommendation (B) [17]

only 0.8% patients responding optimally to further drug trials [8]. The response to the first medication is a strong predictor of future seizure control.

Non-pharmacological treatment

Medically intractable or refractory epilepsy is defined as a failure of adequate trials of two tolerated and appropriately chosen antiepileptic medication schedules with adequate doses [9]. In those patients with intractable epilepsy, other alternative non-pharmacological treatment can be considered including epilepsy surgery, neurostimulation therapy, and diet therapy such as the ketogenic diet. Epilepsy surgery may include focal resective surgery, multiple subpial transections, anterior corpus callosotomy, or hemispherectomy [21].

Neurostimulation therapies include the vagal nerve stimulation (VNS), responsive neurostimulator (RNS) and other investigational neurostimulation modalities [21,32].

Among medically intractable seizure patients, epilepsy surgery is most commonly considered if they have an identifiable seizure focus which is amenable to resection. Epilepsy surgery is an effective and safe alternative form of therapy for those patients with focal onset epilepsy [32,42-51]. Major complications from epilepsy surgery and subdural electrode evaluation have an incidence of less than 7% and long term permanent deficits have an incidence of less than 2% [52-58]. An epilepsy surgery evaluation typically starts with long term video-EEG monitoring to confirm the diagnosis and type of focal onset epilepsy, establish the seizure type and seizure onset zone and determine the disabling effects of ictal behavior [42,59]. In addition, various neuro-radiological imaging techniques are employed to further identify the structural or functional epileptogenic lesion(s). Multiple studies have shown that the prognosis of epilepsy surgery varies depending on the etiology and location of the epileptogenic zone [43-51,60-64]. Radiographically identifiable epileptogenic lesions provide information about the etiology and localization of epilepsy, and can provide prognostic information for focal respective epilepsy surgery. Identifying a structural lesion on MRI provides an excellent prognosis from epilepsy surgery, with 60-90% freedom from disabling seizures [43-51,60-64]. Temporal lobe epilepsy is the most common type of epilepsy, and mesial temporal sclerosis (MTS) is the most common temporal lobe epilepsy [65]. MTS, which can be readily identified on MRI with hippocampal atrophy and increased signal, is known to be medically refractory, but does respond well to anterior temporal lobectomy with better postoperative outcomes than other forms of temporal lobe epilepsy [10,43-48,50,61,63]. When MRI fails to detect a potentially epileptogenic lesion, the chances of an excellent surgical outcome are significantly lower, ranging from 20-65% [40-44]. This may reflect the difficulty in localizing and resecting the epileptogenic zone [60]. In order to improve the radiographic detection of epileptogenic lesions, more advanced imaging techniques have been used such as 7T MRI, volumetric analysis, Diffusion Tensor Imaging (DTI), arterial spin labeling and PET [38,66-74]. However, it is currently unknown if such techniques willimprove outcomes.

Accurate localization of the seizure focus is a key component for successful surgical resection [32,42,58,64]. Despite extensive preoperative testing, placement of subdural grid electrodes (SDGE) and depth electrodes (DE) for invasive EEG monitoring is often needed when non-invasive studies have discordant data or fail to show possible seizure foci and areas of eloquent cortex [32,42,58]. SDGE and DE invasive EEG monitoring can help localize the focus of seizures to better delineate the area or areas that need to be resected (Table 3).

Epilepsy Surgery Techniques	Neurostimulation	Diet Therapy
Focal Resection	Vagal Nerve Stimulation	Ketogenic Diet
Multiple Subpial Transection	Responsive Neurostimulation	Adkins Diet
Corpus Callosotomy	Investigational therapy	Modified Adkins Diet
Hemisphrectomy	Deep Brain Stimulation	Others with low glycemic index
	Transcranial Magnetic Stimulation	
	Electroconvulsive Therapy	

Table 3: Summary of Non-pharmacological Epilepsy Treatment

Conclusion

Although epilepsy only affects 1-3% of the US population, the economic burden and cumulative fatality are significant. Various diagnostic tools are used to find the etiology, type, and location of epileptic foci. It is important to have an accurate diagnosis and to start appropriate treatment. Despite29 different antiepileptic medications available in the US, one third of patients remain refractory to pharmacologic treatment. In those patients, other treatments should be considered to improve the quality of life and decrease morbidity and mortality.

References

1. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, et al. (2005) Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 46: 470-472.
2. Hauser WA, Annegers JF, Rocca WA (1996) Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. See comment in PubMed Commons below Mayo Clin Proc 71: 576-586.
3. Giussani G, Cricelli C, Mazzoleni F, Cricelli I, Pasqua A, et al. (2014) Prevalence and Incidence of Epilepsy in Italy Based on a Nationwide Database. See comment in PubMed Commons below Neuroepidemiology 43: 228-232.
4. Begley CE, Famulari M, Annegers JF, Lairson DR, Reynolds TF, et al. (2000) The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. See comment in PubMed Commons below Epilepsia 41: 342-351.
5. Begley CE, Beghi E (2002) The economic cost of epilepsy: a review of the literature. See comment in PubMed Commons below Epilepsia 43 Suppl 4: 3-9.
6. Hitiris N, Mohanraj R, Norrie J, Brodie MJ (2007) Mortality in epilepsy. See comment in PubMed Commons below Epilepsy Behav 10: 363-376.
7. Sillanpää M, Shinnar S (2010) Long-term mortality in childhood-onset epilepsy. See comment in PubMed Commons below N Engl J Med 363: 2522-2529.
8. Mohanraj R, Brodie MJ (2006) Diagnosing refractory epilepsy: response to sequential treatment schedules. European journal of neurology : the official journal of the European Federation of Neurological Societies 2006;13:277-82.
9. Sinha S, Siddiqui KA (2011) Definition of intractable epilepsy. See comment in PubMed Commons below Neurosciences (Riyadh) 16: 3-9.
10. Perry MS, Duchowny M (2013) Surgical versus medical treatment for refractory epilepsy: outcomes beyond seizure control. See comment in PubMed Commons below Epilepsia 54: 2060-2070.
11. Baker GA, Taylor J, Aldenkamp AP; SANAD group (2011) Newly diagnosed epilepsy: cognitive outcome after 12 months. See comment in PubMed Commons below Epilepsia 52: 1084-1091.
12. Baxendale S, Heaney D, Thompson PJ, Duncan JS (2010) Cognitive consequences of childhood-onset temporal lobe epilepsy across the adult lifespan. See comment in PubMed Commons below Neurology 75: 705-711.
13. Bell GS, Sinha S, Tisi Jd, Stephani C, Scott CA, et al. (2010) Premature mortality in refractory partial epilepsy: does surgical treatment make a difference? See comment in PubMed Commons below J Neurol Neurosurg Psychiatry 81: 716-718.
14. Dupont S, Tanguy ML, Clemenceau S, Adam C, Hazemann P, et al. (2006) Long-term prognosis and psychosocial outcomes after surgery for MTLE. See comment in PubMed Commons below Epilepsia 47: 2115-2124.

15. Shackleton DP, Kasteleijn-Nolst Trenité DG, de Craen AJ, Vandenbroucke JP, Westendorp RG (2003) Living with epilepsy: long-term prognosis and psychosocial outcomes. See comment in PubMed Commons below Neurology 61: 64-70.

16. Stavem K, Guldvog B (2005) Long-term survival after epilepsy surgery compared with matched epilepsy controls and the general population. See comment in PubMed Commons below Epilepsy Res 63: 67-75.

17. Taylor J, Baker GA (2010) Newly diagnosed epilepsy: cognitive outcome at 5 years. See comment in PubMed Commons below Epilepsy Behav 18: 397-403.

18. Trinka E, Bauer G, Oberaigner W, Ndayisaba JP, Seppi K, et al. (2013) Cause-specific mortality among patients with epilepsy: results from a 30-year cohort study. See comment in PubMed Commons below Epilepsia 54: 495-501.

19. Helmstaedter C, Aldenkamp AP, Baker GA, Mazarati A, Ryvlin P, et al. (2014) Disentangling the relationship between epilepsy and its behavioral comorbidities - the need for prospective studies in new-onset epilepsies. Epilepsy & behavior : E&B 31: 43-47.

20. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, et al. (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. See comment in PubMed Commons below Epilepsia 51: 676-685.

21. Shneker BF, Fountain NB (2003) Epilepsy. See comment in PubMed Commons below Dis Mon 49: 426-478.

22. Bien CG (2013) Value of autoantibodies for prediction of treatment response in patients with autoimmune epilepsy: review of the literature and suggestions for clinical management. See comment in PubMed Commons below Epilepsia 54 Suppl 2: 48-55.

23. Chen SJ (2013) Immune-mediated limbic encephalitis-tip of the iceberg in childhood autoimmune epilepsy. See comment in PubMed Commons below Pediatr Neonatol 54: 217-218.

24. Davis R, Dalmau J (2013) Autoimmunity, seizures, and status epilepticus. See comment in PubMed Commons below Epilepsia 54 Suppl 6: 46-49.

25. Weber YG, Nies AT, Schwab M, Lerche H (2014) Genetic biomarkers in epilepsy. See comment in PubMed Commons below Neurotherapeutics 11: 324-333.

26. Pandolfo M (2013) Pediatric epilepsy genetics. See comment in PubMed Commons below Curr Opin Neurol 26: 137-145.

27. Irani SR, Bien CG, Lang B (2011) Autoimmune epilepsies. See comment in PubMed Commons below Curr Opin Neurol 24: 146-153.

28. Bien CG, Scheffer IE (2011) Autoantibodies and epilepsy. See comment in PubMed Commons below Epilepsia 52 Suppl 3: 18-22.

29. Craven I, Griffiths PD, Hoggard N (2011) Magnetic resonance imaging of epilepsy at 3 Tesla. See comment in PubMed Commons below Clin Radiol 66: 278-286.

30. Bronen RA, Fulbright RK, Spencer DD, Spencer SS, Kim JH, et al. (1996) Refractory epilepsy: comparison of MR imaging, CT, and histopathologic findings in 117 patients. See comment in PubMed Commons below Radiology 201: 97-105.

31. Scott CA, Fish DR, Smith SJ, Free SL, Stevens JM, et al. (1999) Presurgical evaluation of patients with epilepsy and normal MRI: role of scalp video-EEG telemetry. See comment in PubMed Commons below J Neurol Neurosurg Psychiatry 66: 69-71.

32. Cascino GD (2004) Surgical treatment for epilepsy. See comment in PubMed Commons below Epilepsy Res 60: 179-186.

33. Henry TR, Babb TL, Engel J Jr, Mazziotta JC, Phelps ME, et al. (1994) Hippocampal neuronal loss and regional hypometabolism in temporal lobe epilepsy. See comment in PubMed Commons below Ann Neurol 36: 925-927.

34. O'Brien TJ, So EL, Mullan BP, Hauser MF, Brinkmann BH, et al. (1998) Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. See comment in PubMed Commons below Neurology 50: 445-454.

35. Chassoux F, Rodrigo S, Semah F, Beuvon F, Landre E, et al. (2010) FDG-PET improves surgical outcome in negative MRI Taylor-type focal cortical dysplasias. See comment in PubMed Commons below Neurology 75: 2168-2175.

36. Chandra PS, Salamon N, Huang J, Wu JY, Koh S, et al. (2006) FDG-PET/MRI coregistration and diffusion-tensor imaging distinguish epileptogenic tubers and cortex in patients with tuberous sclerosis complex: a preliminary report. Epilepsia 47: 1543-1549.

37. Salamon N, Kung J, Shaw SJ, Koo J, Koh S, et al. (2008) FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy. See comment in PubMed Commons below Neurology 71: 1594-1601.

38. Rubí S, Setoain X, Donaire A, Bargalló N, Sanmartí F, et al. (2011) Validation of FDG-PET/MRI coregistration in nonlesional refractory childhood epilepsy. See comment in PubMed Commons below Epilepsia 52: 2216-2224.

39. Stefan H, Rampp S, Knowlton RC (2011) Magnetoencephalography adds to the surgical evaluation process. See comment in PubMed Commons below Epilepsy Behav 20: 172-177.

40. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, et al.(2013) Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 54: 551-563.

41. Schmidt D, Schachter SC (2014) Drug treatment of epilepsy in adults. See comment in PubMed Commons below BMJ 348: g254.

42. Cascino GD (2011) From the American Epilepsy Society 2009 Annual Course. Non-substrate-directed epilepsy and surgery: PRO and CON. See comment in PubMed Commons below Epilepsy Behav 20: 190-193.

43. Engel J Jr, McDermott MP, Wiebe S, Langfitt JT, Stern JM, et al. (2012) Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. See comment in PubMed Commons below JAMA 307: 922-930.

44. de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, et al. (2011) The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. See comment in PubMed Commons below Lancet 378: 1388-1395.

45. Benifla M, Rutka JT, Otsubo H, Lamberti-Pasculli M, Elliott I, et al. (2008) Long-term seizure and social outcomes following temporal lobe surgery for intractable epilepsy during childhood. See comment in PubMed Commons below Epilepsy Res 82: 133-138.

46. Engel J, Wiebe S, French J, Sperling M, Williamson P, et al. (2003) Practice parameter: temporal lobe and localized neocortical resections for epilepsy. Epilepsia 44: 741-751.

47. Ansari SF, Tubbs RS, Terry CL, Cohen-Gadol AA (2010) Surgery for extratemporal nonlesional epilepsy in adults: an outcome meta-analysis. See comment in PubMed Commons below Acta Neurochir (Wien) 152: 1299-1305.

48. Lowe AJ, David E, Kilpatrick CJ, Matkovic Z, Cook MJ, et al. (2004) Epilepsy surgery for pathologically proven hippocampal sclerosis provides long-term seizure control and improved quality of life. See comment in PubMed Commons below Epilepsia 45: 237-242.

49. Haneef Z, Stern J, Dewar S, Engel J Jr (2010) Referral pattern for epilepsy surgery after evidence-based recommendations: a retrospective study. See comment in PubMed Commons below Neurology 75: 699-704.

50. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group (2001) A randomized, controlled trial of surgery for temporal-lobe epilepsy. See comment in PubMed Commons below N Engl J Med 345: 311-318.

51. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, et al. (2003) Initial outcomes in the Multicenter Study of Epilepsy Surgery. See comment in PubMed Commons below Neurology 61: 1680-1685.

52. Van Gompel JJ1, Worrell GA, Bell ML, Patrick TA, Cascino GD, et al. (2008) Intracranial electroencephalography with subdural grid electrodes: techniques, complications, and outcomes. See comment in PubMed Commons below Neurosurgery 63: 498-505.

53. Hedegard E, Bjellvi J, Edelvik A, Rydenhag B, Flink R, et al. (2014) Complications to invasive epilepsy surgery workup with subdural and depth electrodes: a prospective population-based observational study. Journal of neurology, neurosurgery, and psychiatry 85: 716-720.

54. Wellmer J, von der Groeben F, Klarmann U, Weber C, Elger CE, et al. (2012) Risks and benefits of invasive epilepsy surgery workup with implanted subdural and depth electrodes. See comment in PubMed Commons below Epilepsia 53: 1322-1332.

55. Yuan J, Chen Y, Hirsch E (2012) Intracranial electrodes in the presurgical evaluation of epilepsy. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 33: 723-729.

56. Lesser RP, Crone NE, Webber WR (2010) Subdural electrodes. See comment in PubMed Commons below Clin Neurophysiol 121: 1376-1392.

57. MacDougall KW, Burneo JG, McLachlan RS, Steven DA (2009) Outcome of epilepsy surgery in patients investigated with subdural electrodes. See comment in PubMed Commons below Epilepsy Res 85: 235-242.

58. Shah AK, Mittal S2 (2014) Invasive electroencephalography monitoring: Indications and presurgical planning. See comment in PubMed Commons below Ann Indian Acad Neurol 17: S89-94.

59. Cambier DM, Cascino GD, So EL, Marsh WR (2001) Video-EEG monitoring in patients with hippocampal atrophy. See comment in PubMed Commons below Acta Neurol Scand 103: 231-237.

60. Noe K, Sulc V, Wong-Kisiel L, Wirrell E, Van Gompel JJ, et al. (2013) Long-term outcomes after nonlesional extratemporal lobe epilepsy surgery. See comment in PubMed Commons below JAMA Neurol 70: 1003-1008.

61. Bell ML, Rao S, So EL, Trenerry M, Kazemi N, et al. (2009) Epilepsy surgery outcomes in temporal lobe epilepsy with a normal MRI. See comment in PubMed Commons below Epilepsia 50: 2053-2060.

62. Bien CG, Szinay M, Wagner J, Clusmann H, Becker AJ, et al. (2009) Characteristics and surgical outcomes of patients with refractory magnetic resonance imaging-negative epilepsies. See comment in PubMed Commons below Arch Neurol 66: 1491-1499.

63. Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, Wiebe S (2010) Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. See comment in PubMed Commons below Epilepsy Res 89: 310-318.

64. Immonen A, Jutila L, Muraja-Murro A, Mervaala E, Äikiä M, et al. (2010) Long-term epilepsy surgery outcomes in patients with MRI-negative temporal lobe epilepsy. See comment in PubMed Commons below Epilepsia 51: 2260-2269.

65. Wiebe S (2000) Epidemiology of temporal lobe epilepsy. See comment in PubMed Commons below Can J Neurol Sci 27 Suppl 1: S6-10.

66. Madan N, Grant PE (2009) New directions in clinical imaging of cortical dysplasias. See comment in PubMed Commons below Epilepsia 50 Suppl 9: 9-18.

67. Pan JW, Duckrow RB, Gerrard J, Ong C, Hirsch LJ, et al. (2013) 7T MR spectroscopic imaging in the localization of surgical epilepsy. See comment in PubMed Commons below Epilepsia 54: 1668-1678.

68. Derix J, Yang S, Lüsebrink F, Fiederer LD, Schulze-Bonhage A, et al. (2014) Visualization of the amygdalo-hippocampal border and its structural variability by 7T and 3T magnetic resonance imaging. See comment in PubMed Commons below Hum Brain Mapp 35: 4316-4329.

69. Lopez-Acevedo ML, Martinez-Lopez M, Favila R, Roldan-Valadez E (2012) Secondary MRI-findings, volumetric and spectroscopic measurements in mesial temporal sclerosis: a multivariate discriminant analysis. Swiss medical weekly 142: w13549.

70. Mueller CA, Scorzin J, von Lehe M, Fimmers R, Helmstaedter C, et al. (2012) Seizure outcome 1 year after temporal lobe epilepsy: an analysis of MR volumetric and clinical parameters. See comment in PubMed Commons below Acta Neurochir (Wien) 154: 1327-1336.

71. Coan AC, Morita ME, Campos BM, Bergo FP, Kubota BY, et al. (2013) Amygdala enlargement occurs in patients with mesial temporal lobe epilepsy and hippocampal sclerosis with early epilepsy onset. See comment in PubMed Commons below Epilepsy Behav 29: 390-394.

72. Singh P, Kaur R, Saggar K, Singh G, Kaur A (2013) Qualitative and quantitative hippocampal MRI assessments in intractable epilepsy. See comment in PubMed Commons below Biomed Res Int 2013: 480524.

73. Vargas MI, Becker M, Garibotto V, Heinzer S, Loubeyre P, et al. (2013) Approaches for the optimization of MR protocols in clinical hybrid PET/MRI studies. See comment in PubMed Commons below MAGMA 26: 57-69.

74. Garibotto V, Heinzer S, Vulliemoz S, Guignard R, Wissmeyer M, et al. (2013) Clinical applications of hybrid PET/MRI in neuroimaging. See comment in PubMed Commons below Clin Nucl Med 38: e13-18.