EPILEPSY UPDATE IN 6 CASES

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Case
A 26-year old male who works as a welder is referred by the primary care physician for brief confusional episodes. These episodes have been:

- Present for 6 years often unaware
- He drive 10 miles to work daily
- Has a history of an initial tonic-clonic seizure one year ago. He reported milder episodes with treatment. His last convulsion was 4 months ago after he missed a dose of levetiracetam that had been prescribed to him. He has no warning during these episodes. His wife has observed 1-2 minute episodes of staring, dazed behavior with fumbling and chewing. He had one unexplained car crash the previous year.

He has been treated with carbamazepine extended release 400 mg twice a day with persisting seizures and became dizzy on 500 mg twice a day. He has a history of an MRI done locally 3 years ago, which was read as normal and recent EEG, which was also interpreted as normal. His past medical history has no neurological injuries, no family history of seizures. He is often unaware of these episodes. His wife reports him having approximately 3-4 events a month.

On a follow-up visit you increase his carbamazepine to 1200 mg a day, he continues to have 2 mild complex partial seizures every few weeks, 1-2 minutes of confusion, but with no convulsions. He feels sedated and dizzy. He has been counseled not to drive until seizures are controlled. He asks about treatment options so he can continue working and driving and possibly.

Antiepileptic drug Advances
There are now 24 antiepileptic drugs (AEDs) approved for use in epilepsy in the United States (US) by the Food and Drug Administration (FDA) in addition to 2 stimulation devices, 1 new surgical procedure and 2 diets. Five of the AEDs have come onto the market within the past 2 years. Below is a table of the newest medications most recently approved for epilepsy.

Antiepileptic Drugs and Devices Currently Approved by the USA FDA

Pre 1993	1993-2005	2006-2011
Carbamazepine	Felbamate	Clobazam
Clonazepam	Gabapentin	Ezogabine
Diazepam	Lamotrigine	Lacosamide
Ethosuccimide	Levetiracetam	Rufinamide
Lorazepam	Oxcarbazepine	Vigabatrin
Phenobarbital	Pregabalin	
Phenytoin	Tiagabine	
Primidone	Topiramate	
Valproic acid	Vagus nerve stimulation	
	Zonisamide	

** Perampanel was also approved in December 2012 and Brivaracetam in 2016.

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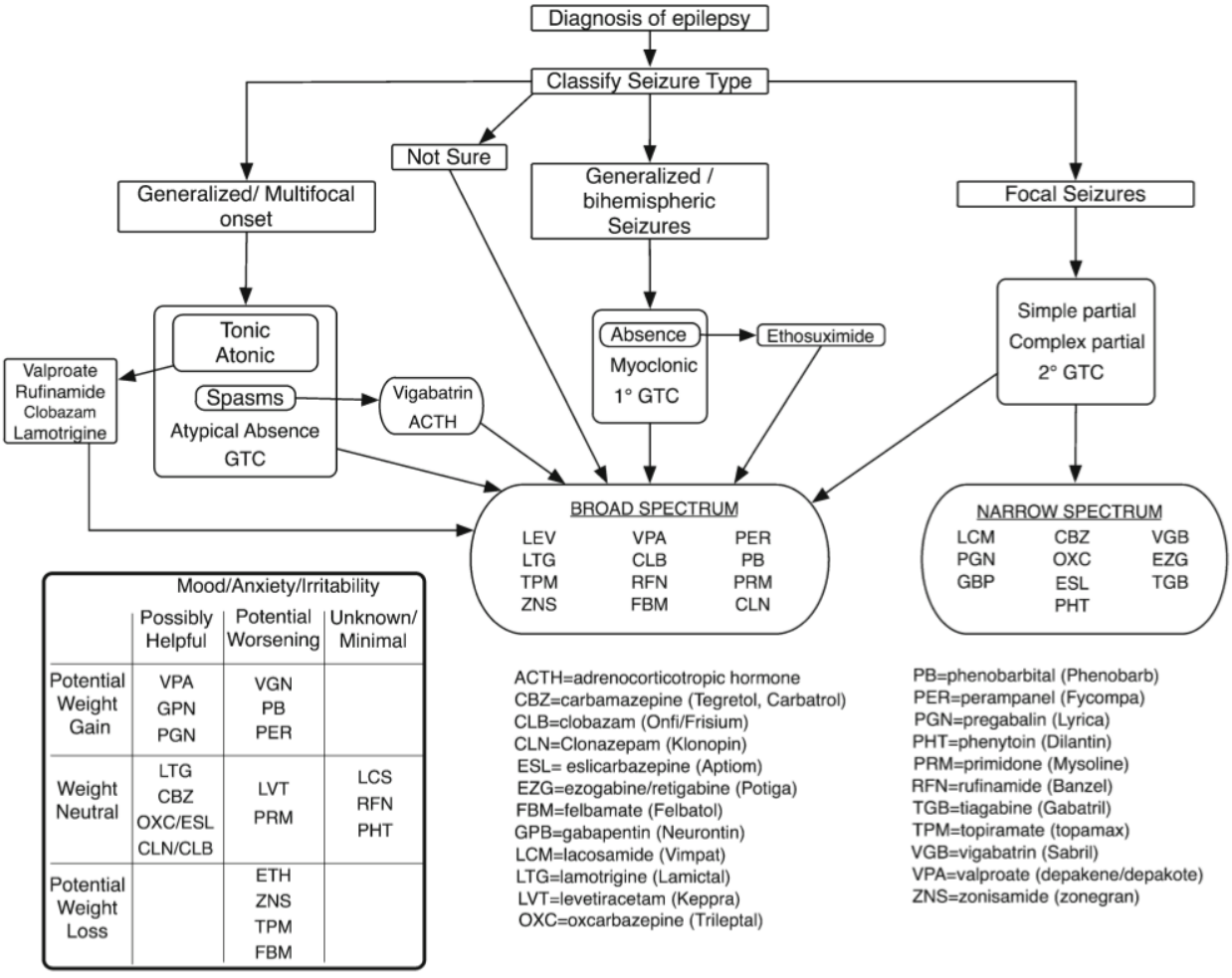
AEDS Recently Approved (Reference 21)

AED	*FDA Indication*	*Putative Mechanism*
Clobazam	**Lennox-Gastaut syndrome**	**GABA(A) binding**
Eslicarbazepine acetate	**Add-on for partial epilepsy**	**Sodium channel Modulation**
Ezogabine	**Add-on for partial epilepsy**	**Potassium channel modulation**
Lacosamide	**Add-on for partial epilepsy**	**Sodium channel modulation**
Perampanel	**Add- on for partial epilepsy**	**AMPA antagonist**
Rufinamide	**Atonic seizures**	**Sodium channel modulation**
Vigabatrin	**Infantile spasms/Add-on for partial epilepsy**	**Irreversible inhibition of GABA transaminase**
Brivaracetam	**Add – on for partial epilepsy**	**SV2- A binding**

An algorithm for choosing seizure medications is proposed.



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Case
An 18-year old male has a lifelong history of refractory epilepsy. She has multiple handicaps; she has developmental delay. She has a history of cerebral palsy that presents with spastic diplegia, but remains ambulatory. She has a history of infantile spasms that responded to ACTH. They are seeking to establish care you as the family recently moved from a previous state.

The seizure types are poorly described, but include the following:

- Drop spells in which the patient falls
- Convulsions, unsure if they are one or both sides
- Staring into space, recovery taking several minutes
- Stiffens with tremors, mostly during sleep
- Some days the patient seems to daze for hours blinking and staring
- Multiple episodes of status epilepticus and seizure clusters

The patient has been treated with 8 antiepileptic drugs in the past. Currently is on levetiracetam, valproate and carbamazepine. Six years ago, imaging revealed a question of generalized atrophy, but no overt lesions.

Lennox- Gastaut Syndrome
Lennox Gastaut syndrome is a severe difficult to treat epilepsy of childhood onset.- typically less than 8 years of age. It is more common in males than females. It accounts for 3- 11% of all childhood epilepsies. It can evolve from infantile spasms and encephalopathic epilepsy. It frequently persists until childhood. The ILAE defines Lennox Gastaut syndrome as a syndrome characterized by childhood onset, multiple seizures types most commonly tonic, atonic and atypical absence. However, focal and myoclonic seizures can occur. There is a characteristic EEG pattern consisting of diffuse slow spike and slow wave activity and bursts of fast rhythm during sleep. There are numerous co morbidities associated with this syndrome, which includes psychomotor delay, behavioral disorders or both.

Management of LGS in adulthood is problematic due to the relative intractability of the seizures, complexity of intellectual and development issues and the social effects of disabilities and behavioral problems. Treatment approaches to LGS include pharmacotherapy with AEDs. Commonly used AEDs include Felbamate, lamotrigine, topiramate, rufinamide and clobazam. Non-pharmacological therapies include diets such as the ketogenic or modified Atkins diet. These diets have shown nearly a 50-60% reduction ins seizure frequency. Surgical approaches such as callosotomy or vagus nerve stimulation is also useful in this situation.

Cannabis
Of the 400 + coumpounds found in cannabis, there are 2 main groups of coumpounds salient to epilepsy. THC is the psychoactive compound which is not believed to have any impact on epilepsy. However Cannabidiol may have a role in seizure control. Currently, there has been consideration of using special strains of cannabis (high cannebidiol strains of cannabis for LGS.

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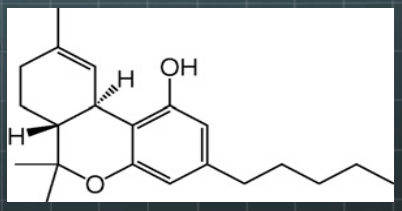
Exogenous Cannabinoids

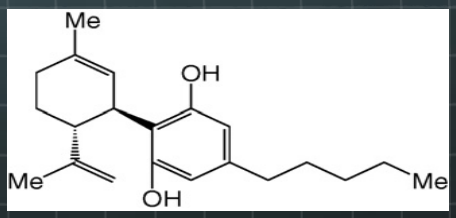
Δ^9 Tetrahydrocannabinol (THC)

Psychoactive
CB1 agonist

Cannabidiol (CBD)

Non-psychoactive
Very slight CB1/CB2 indirect antagonist; opposes some CNS effects of THC
Antagonist at GPR55 receptor, ? CBD receptor





Clinical research trials are currently underway to assess the use of cannabis based compounds. Previous observational trials of cannabis for epilepsy is listed below.

Four Controlled CBD Trials in Epilepsy

STUDY	INCLUSION CRITERIA Notes	PTS	DOSE TIME	EFFICACY	SAFETY
Mechoulam (1978)	TLE/TRE Groups not matched; AEDs, no stats	9 4 CBD 5 PLA	200/d x 3 mos	5 Rx'd: 2 Sz free, better, unchanged 4 Placebo: unchanged	No adverse events
Cunha (1980)	TLE/TRE >= TCSz/wk DB?	15 7 CBD 8 PLA	200-300 mg/d 3-18 wks	4 CBD seizure free; control seizure free	Seizure-free: 1 placebo 4 CBD
Ames (1985)	Residential/ MR/TRE -baseline data	12 ? CBD v PLA	200 mg/d x 4wks	No group differences	Mild drowsiness
Trembly (1990)	TRE adults Conflict of 90 paper and 92 chapter	12 ? CBD v PLA	PLAC x 6 mos, CBD 300/dy x 6 mos	No group differences on seizures or cogn-behavior tasks	No data

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A 2013 Cochrane review (23) of AEDs used for Lennox Gastaut syndrome found a significant amount of heterogeneity in the studies that have assessed seizure medications for LGS. As a result, no meta-analysis could be performed. The authors concluded that there is no ideal treatment for LGS. No study has shown the superiority of one drug. Rufinamide, lamotrigine, topiramate and Felbamate are useful as add- on therapy and clobazam may help reduce atonic seizures.

The main goals of LGS extend beyond seizure control. They include reduce polypharmacy, minimizing drug side effects, managing behavioral and cognitive comorbidities and providing support for social and developmental needs.

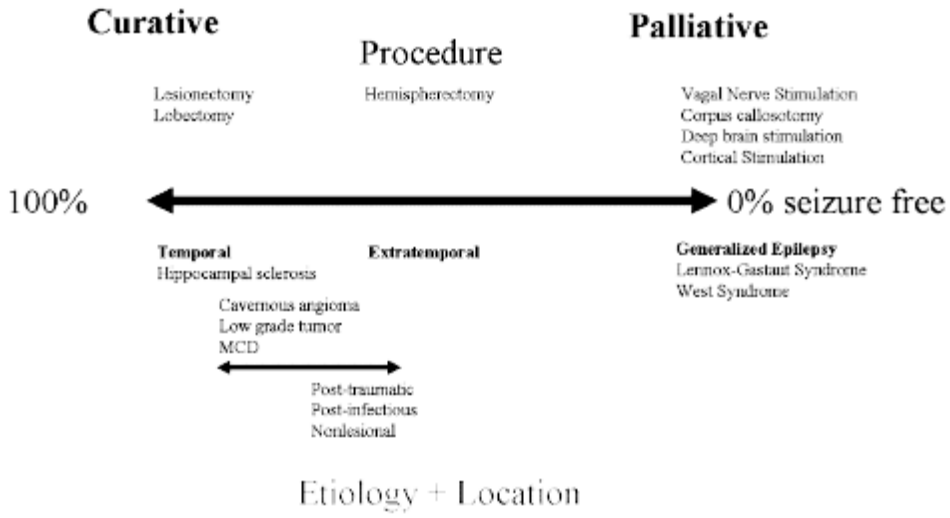
LGS remains one of the most challenging epileptic encephalopathies despite availability of several new AEDs. Long term outcome regarding seizure control and intellectual development is disappointing and can be taxing for families. The management of LGS into adulthood requires global care. Total seizure control is not the main goal as opposed to management of comorbidities and maintaining quality of life.

Case #6

A 29-year old woman reports seizures starting at 12-years. They occurred from age 12- 14-years and then resumed at age 18-years to present. Seizures begin with a rising epigastric sensation, followed by loss of awareness, lip smacking for 1-2 minutes, occurs 3-5 times per month. The patient had been treated with lamotrigine 400 mg daily previously, levetiracetam 2000 mg daily. There are no risk factors for epilepsy. She works as a secretary. Her neurological examination is normal. Her EEG is as noted below. Her routine lab tests have been normal an MRI performed at our own hospital is otherwise normal. Given that the patient has failed 2 seizure medications and assuming compliance with medications, she fits the criteria for intractable epilepsy.

The ILAE defines drug resistant epilepsy as a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. When a patient is deemed as drug resistant by the neurologist, surgical candidacy should be assessed.

Figure 1 Surgical interventions



Surgical Options

What are the surgical options that are available? There are a number of different procedures that are available for surgical management of epilepsy. Figure 1 illustrates a diagram outlining the continuum of epilepsy surgeries from curative to palliative[6]. The choice of procedure will depend on the underlying pathology. A simple classification dichotomy involves epilepsies, which are related to a particular lesion, or lesional epilepsy. In these patients, imaging studies have detected a specific intra-axial structural abnormality suggesting the likely site of seizure onset and surgical pathology. Examples of lesional epilepsies include mesial temporal sclerosis, neoplasms, cavernous hemangioma, and other types of pathology. In these patients, focal cortical resection can be offered to these individuals. The most common operative procedure is focal corticectomy defined as resection

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of the epileptic brain tissue. The most common location for this is the anterior temporal lobe commonly known as anterior temporal lobectomy. The rationale for surgical treatment is the excision of the epileptogenic tissue or zone which is the site of seizure onset and initial seizure propagation. Individuals that undergo this procedure have to undergo a presurgical evaluation which is designed to confirm the epileptogenicity of the imaging abnormality in order to proceed with focal cortical resection.

Mesial temporal lobe epilepsy is common, medically intractable, and the most amenable to surgical intervention. An estimated 100,000-200,000 individuals with intractable epilepsy in the United States have mesial temporal lobe epilepsy[1]. A review of multiple studies has shown that almost two-thirds of the patients with intractable mesial temporal lobe epilepsy become seizure free after surgical treatment[3]. In general, patients with hippocampal atrophy, unilateral epileptiform discharges predicted from concordant MRI and EEG studies has an excellent surgical outcome with over 90% of these patients becoming seizure free[3]. Younger patients having surgery earlier gained a benefit of having a more improved quality of life from not having to deal with the stigma and problems associated with seizures. Extratemporal neocortical epilepsy with a well circumscribed lesion such as a low grade neoplasm or cavernous malformation is predictive of a seizure free outcome in almost 70-80% of patients[3].

For lesions that are less well circumscribed such as cortical dysplasias, the seizure free outcome rate is approximately 40-55%[3]. Cortical malformations are often extratemporally located and require more intensive presurgical evaluations in order to confirm the exact area of epileptogenicity. Twenty to fifty percent of patients with intractable partial epilepsy have a normal MRI and they may be able to undergo surgical treatment based on other forms of physiologic studies such as SPECT scans, SISCOM, PET, MEG, and MRS. The outcome of patients with nonlesional or normal MRI epilepsy compares favorably to extratemporal seizure disorders. Individuals with normal MRI studies may benefit from functional neuroimaging and may require chronic intracranial EEG monitoring.

Corpus Callosotomy
Corpus callosotomy is recommended for children and adults with symptomatic generalized epilepsy. Lennox-Gastaut syndrome, disabling atonic and/or tonic seizures may also be candidates for this procedure. Seizures severely limit the daily activity of these patients because of sudden falls and head injury. Corpus callosotomy is palliative in nature and does not render its patients seizure-free. It will reduce seizures in 70% of patients while 30% show substantial improvement[7]. Partial seizures may occur, but without patients falling down. After corpus callosotomy most patients have improved cognitive function, activities of daily living, and behavior. Outcome is better with complete callosotomy than with an anterior 2/3rd callosotomy but there is a greater risk of a disconnection syndrome in those patients[6].

Hemispherectomy/Functional Hemispherectomy
This particular procedure is reserved for infants and children with catastrophic epilepsy, developmental regression, and a unilateral hemiparesis, particularly of the hand. This surgery can have a seizure-free outcome reported between 53-67% and is most successful in patients with non-cortical development pathology[7]. This surgery has also been found to improve IQ scores in patients who have seizure reduction. Large studies from major centers have reported a seizure-free outcome rate of 64% at two years after surgery with or without cortical dysplasia[8]. After an interval of two to five years, 25% of the patients with cortical dysplasia can have recurrent seizures.

Radiosurgery
Radiosurgery with gamma knife is utilized in patients with focal epilepsy when the seizure focus is located in eloquent or surgically challenging brain regions, which are associated with unacceptable high incidence of complications[9-11]. Extensive experience exists for lesional epilepsy associated with arteriovenous malformations, cavernomas, and tumors. This procedure has been used with good results for patients with mesial temporal sclerosis and hypothalamic hamartomas[9-11]. Outcomes from these procedures tend to be delayed with benefits noted in 1-2 years after surgery.

Thermal ablation (Visualase®)
Thermal ablation is a novel FDA approved means of resection of lesional epilepsy. Visualase utilizes light energy (laser) to destroy soft tissue including tumor or damaged tissue. Laser energy is delivered to the target area (the

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lesion) using a laser probe. As light is delivered through the laser probe temperatures in the target area begin to rise, destroying the lesion. Because Visualase procedures are guided by MRI images, the procedure can provide precise targeting. The procedure is minimally invasive and it tends to lead shorter hospital stays.

Neuromodulation (RNS®)
In November 2013, the US FDA approved a new device for the management of drug resistant epilepsy. This device is a closed loop stimulator that is implanted within the skull but is attached to either a 4 contact strip EEG electrode or 4 point depth EEG electrode that extends from the device to the targeted cortical area responsible for the seizures. The device is programmed to detect individual seizures as recorded by the intracranial EEG and then is able to deliver targeted stimulation to the responsible neurons. The RNS System has been evaluated in three clinical trials, including a prospective, randomized, double-blinded, sham stimulation controlled pivotal study. The pivotal study primary effectiveness endpoint was met by demonstrating a 37.9 percent reduction in seizure frequency in patients treated with responsive stimulation compared to a 17.3 percent reduction in patients who were implanted with the device but were not receiving responsive stimulation during a three month blinded period. The difference is statistically significant (p=0.012). For those subjects who reached two years post-implant, 55 percent of the subjects experienced a 50 percent or greater reduction in seizures.

Surgical Outcomes and Risks
There has been an explosion in the popularity of epilepsy surgery with several thousand operations performed yearly. This has been accompanied by a growing volume of literature reporting outcome statistics. The most common operation, anterior temporal lobectomy, offers a seizure-free rate of 70-90% leading to improvements in quality of life measures such as improved employability, ability to drive, marital rates, and most important, reduction in mortality rates[3,12-17]. One recent analysis performed a systematic review of the literature regarding anterior temporal lobectomy outcomes utilizing Monte Carlo simulation models and reported that anterior temporal resection increases survival by 5 years and increases quality adjusted life expectancy by 7.5 quality adjusted life years. Surgery was preferred over medical management in 100% of the simulations.[18] Cortical resection of extratemporal lesions results in a somewhat lower seizure-free rate ranging from 40-60% depending on the type of surgery. Corpus callosotomy, a palliative procedure, benefits 50-80% of patients yet elimination of seizure disorder is rare[7].

Good health outcomes can be achieved with low surgical complication rates provided careful selection of patients is combined with technical skill and an experienced team. Some deficits are expected as a result of surgery. Many are transient and resolve. For example, up to 50% or more patients undergoing anterior temporal lobectomy can be expected to have a minor visual field loss[15]. Potentially serious adverse affects include infection, hemorrhage, hemiparesis, aphasia, and psychiatric complications. However, most reports suggest that these complications occur in less than 5% of patients[19]. Patients must be fully apprised of the potential risk and they must make the final decision to proceed. Both physicians and patients must also recognize the risks of not doing surgery, given the potential for elimination of seizures versus the morbidity and mortality of intractable epilepsy.

One of the more concerning adverse effects of epilepsy surgery for both patient and neurologist is memory loss. Oftentimes, the concern about memory function postoperatively can at times lead to avoidance of this procedure. However, a recent study has helped to allay those fears[20]. Langfitt and colleagues evaluated the importance of seizure outcome and memory decline on health-related quality of life (HRQOL) in 138 patients undergoing surgery for partial epilepsy. Fifty patients (36%) experienced a reduction in memory performance after surgery. 113 patients (82%) were seizure free at 2 or 5 years following surgery. 39 of the 113 patients (35%) had a memory decline. The quality of life of the 113 individuals with a favorable seizure outcome improved regardless of any acquired memory loss. Only individuals who failed to respond to surgery and had memory loss (11 patients, 8%) had reduced quality of life scores. The memory loss related to surgery tends to be material specific and not globally amnestic[19].

The patient described in this example case, should be evaluated for potential curative surgery. This patient likely should have had this evaluation after failure of their second medication. As a general rule, any compliant patient who fails to respond after one medication should raise a red flag in the clinician's mind that perhaps the diagnosis in doubt where one is dealing with a patient who is refractory to medications.

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Indeed, surgery is now a standard of care and not an experimental or an option of last resort. There have been randomized, controlled trials; there have been a number of surgical series that have clearly detailed the success of surgical management for epilepsy in selected patient populations. This data is applicable to both adults and children and should be often considered as soon as a patient has had a breakthrough seizure after initiation of an antiepileptic drug.

As you can see there are a number of treatment approaches to manage epilepsy. We need to be familiarize ourselves with these approaches in order to best help our patients with epilepsy. The Institute of Medicine report on epilepsy highlighted the serious delays in delivering treatments to patients with chronic seizures[22]. It is only in understanding what is available and then facilitating access to these therapies will we make headway in improving the quality of life for patients with epilepsy.

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