Clinical Epilepsy

American Epilepsy Society
A seizure is the manifestation of an abnormal, hypersynchronous discharge of a population of cortical neurons. This discharge may produce subjective symptoms or objective signs, in which case it is a clinical seizure, or it may be apparent only on an electroencephalogram (EEG), in which case it is an electrographic (or subclinical) seizure.
Clinical seizure: a discharge producing subjective symptoms or objective signs

Electrographic (subclinical) seizure: apparent only on electroencephalography (EEG)$^1$

Epilepsy: a disorder of recurrent seizures arising from abnormal brain electrical activity. The seizures occur spontaneously, i.e. not provoked by acute systemic or neurologic insults; rather, their recurrence is facilitated by a persistent alteration of brain function promoting neuronal hyperexcitability and hypersynchrony$^2$. In an epileptic brain, seizures occur without provocation, but stressors may increase the likelihood of seizure recurrence (e.g. patients may have seizures when rested, but may be even more likely to have seizures when sleep-deprived, while a normal brain would not have seizures due to sleep deprivation.)

You may watch Dr. Robert Fisher discuss seizures and epilepsy on epilepsy.com, or on Youtube in Understanding Epilepsy (Epilepsy #1): http://www.youtube.com/watch?v=MNQlq004FkE
The incidence of new-onset seizures in the general population is approximately 80 per 100,000 per year; approximately 60% of these patients will have epilepsy, a tendency toward recurrent unprovoked seizures. At least two unprovoked seizures are required for the diagnosis of epilepsy. In the past, physicians were reluctant to make this diagnosis even after repeated seizures, because of the adverse consequences including social stigmatization and limitations on driving and employment. Despite advances in public understanding of the condition, these issues remain active. The euphemism seizure disorder has been frequently employed to avoid the term epilepsy, and may also be used to refer to situations characterized by recurrent seizures where each is provoked by an identifiable stimulus; for example, febrile convulsions. The current definition of epilepsy is the tendency to have repeated seizures (at least two) as a consequence of a brain disorder, that is, unprovoked by an acute systemic or brain insult. This definition stresses that the problem is one of brain function, and that the patient has the potential for more seizures. This definition excludes seizures due to exogenous factors, such as ethanol or sedative drug withdrawal, or to metabolic disorders, such as nonketotic hyperglycemia.

Estimates of the annual incidence of epilepsy in the general population range from 30 to 57 per 100,000. These rates vary with age, being high in infants and young children, then decreasing throughout adulthood until approximately age 60, when they again begin to increase. The overall prevalence of epilepsy is approximately 6 per 1000.
Seizures can be classified based on their clinical and electrographic features. The diagnosis of a patient’s epilepsy syndrome is based on their clinical history and their seizure type(s).
Partial seizures have onset in part of the brain; synonymous terms that are frequently used include localization-related or focal seizures. Partial seizures are divided into two main types, depending on whether or not consciousness is fully preserved. During simple partial seizures, consciousness is preserved; the person is alert, can respond to questions or commands, and can remember what occurred during the seizure. During complex partial seizures, consciousness is altered or lost; the ability to pay attention or respond to questions or commands is thus impaired or lost. Often, there is no memory of what happened during all or part of the complex partial seizure. The distinction between simple and complex partial seizures is critical, because activities such as driving and operating dangerous machinery must be restricted in patients with uncontrolled complex partial seizures; restrictions for people with only simple partial seizures depend on the specific seizure manifestations (and, for driving, on regulations in a particular state). Partial onset seizures may progress to secondarily generalized seizures. Secondly generalized seizures ultimately involve motor activity on both sides of the body and can be difficult to distinguish from primary generalized seizures.
The diverse range of simple partial seizures gives rise to diagnostic challenges. For example, paresthesias (tingling sensations) in the fifth finger spreading to the forearm can result from a seizure, migraine, transient ischemic attack, or ulnar nerve disorder. Sudden abdominal discomfort may be produced by a gastrointestinal disorder as well as by a seizure arising from brain structures subserving autonomic or visceral function. When occurring in isolation, these symptoms may not be recognized as seizures by the patient or doctor.

Motor seizures alter muscle activity. Localized tonic posturing (stiffening) or clonic movements (twitching, jerking) can occur. Abnormal movements may be restricted to one body part or involve gradual spread to adjacent areas on the same side of the body (Jacksonian seizure) or both sides of the body with loss of consciousness (secondarily generalized seizure).

Epileptic discharges that occur in the sensory cortex may produce sensory seizures that manifest as hallucinations or illusions, for example; a sensation of something that is not there or distortion of a true sensation. Hallucinations may remain restricted to one area (e.g., paresthesias in a finger) or spread to other areas (e.g., entire upper extremity or entire side in a Jacksonian sensory march). Hallucinations and illusions can involve any sensory modality, including touch (e.g., pins and needles, electrical sensations), smell or taste (e.g., chemical or metallic sensations, often unpleasant), vision (e.g., flashing lights, complex scene), and hearing (e.g., buzzing, person's voice).

Autonomic seizures are common, evoking changes in autonomic activity (e.g., altered heart or breathing rate, sweating) or visceral sensations (e.g., in abdomen or chest).

Psychic seizures affect how we feel, think, and experience things. Patients may report a "dreamy state," transitional between waking and unconsciousness. Psychic seizures can alter language function, perception or memory. They can also evoke spontaneous emotions (e.g., fear, anxiety, or depression), altered perceptions of time or familiarity (time slowing down or speeding up; déjà vu—new experiences appear familiar, jamais vu—familiar things appear foreign), depersonalization (feeling one is not oneself), derealization (the world seems unreal, dream-like), or autoscopy (viewing one's body from outside).
Complex partial seizures are seizures which are associated with impairment of consciousness. A common misunderstanding is that this requires seizure spread to both sides of the brain. The majority of complex partial seizures originate in the temporal lobe and can affect consciousness while still remaining focal. During complex partial seizures the patient tends to stare off. This is accompanied by impaired responsiveness, cognitive function, and recall, although some degree of responsiveness may be preserved (e.g., orienting toward a stimulus). Automatic movements (automatisms) are common and involve the mouth (e.g., lip smacking, chewing, swallowing), upper extremities (e.g., fumbling, picking), vocalization/verbalization (e.g., grunts, repeating a phrase), or complex acts (e.g., shuffling cards). More dramatic automatisms occasionally occur (e.g., screaming, running, disrobing, pelvic thrusting). Complex partial seizures usually last from 15 seconds to 3 minutes. After the seizure, postictal confusion is common, usually lasting less than 15 minutes, although other symptoms, such as fatigue, may persist for hours.
Partial seizures can progress to generalized seizures with tonic-clonic activity. Once a partial seizure secondarily generalizes it is generally impossible to differentiate from a primarily generalized seizure. The history, electroencephalogram (EEG), neurologic exam (especially postictally), and neuroimaging tests (CT or MRI) often help distinguish these seizure types. In secondarily generalized seizures, patients may recall an aura prior to the convulsive activity or witnesses may observe a simple partial or complex partial seizure prior to generalization. In addition, following a secondarily generalized seizure, the patient may have focal weakness (Todd’s paralysis) on the side contralateral to seizure onset.
The EEG in partial seizures is variable. During simple partial seizures, scalp-recorded EEG may be normal, or show quite localized or lateralized abnormal rhythmic activity. During complex partial seizures, rhythmic activity, which is often bilateral, is seen. During secondarily generalized seizures, rhythmic activity is usually high amplitude, bilateral and diffuse, although it is usually obscured by artifact from the abundant muscle activity characterizing these seizures.
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Generalized seizures affect both cerebral hemispheres from the beginning of the seizure. They produce loss of consciousness, either briefly or for a longer period of time, and are sub-categorized into several major types: absence, myoclonic, atonic, tonic, and tonic-clonic.
Absence (petit mal) seizures are brief episodes, usually lasting 3-20 seconds, of staring with impairment of awareness and responsiveness. There is no warning before the seizure, and immediately afterward the person is alert and attentive. This lack of a postictal period is a key feature that allows one to distinguish between absence and partial complex seizures. If duration is >10 seconds, there are often accompanying motor phenomena (e.g., eye blinks, brief automatic mouth or hand movements, changes in muscle tone). These spells usually begin between ages 4 and 14 years, and usually resolve by age 18. Absence seizures are often provoked by hyperventilation, an effective means of reproducing seizures in the office or during the EEG. The EEG signature of absence epilepsy is the generalized 3 Hz spike-wave discharge. Children with typical absence seizures usually have normal development and intelligence.
The yellow bar in the slide indicates approximately 1 second; generalized 3/second (i.e. 3 Hz) spike/slow wave complexes are noted.
Atypical absence seizures also occur predominantly in children, usually beginning before 6 years of age. As opposed to typical absences, atypical absences may begin and end gradually (over seconds), usually last 5-30 seconds, and are not generally provoked by rapid breathing. The child stares, but the reduction in responsiveness is usually incomplete. Eye blinking or slight twitching movements of the lips may be seen. Because atypical absence seizures often occur in children with global cognitive impairment, the seizures may be difficult to distinguish from the child’s usual behavior. The EEG usually shows generalized slow spike-wave complexes (i.e., <2.5 Hz). Atypical absence seizures usually arise during childhood, but may persist into adulthood. Atonic and tonic seizures often occur in patients with atypical absence seizures.
Atypical Absence Seizures
Myoclonic seizures involve a brief, shock-like jerk of a muscle or group of muscles. Benign myoclonus occurs in healthy people (e.g., while falling asleep). This is not a myoclonic seizure. Pathologic myoclonus can result from epileptic and nonepileptic causes. Epileptic myoclonus usually causes bilateral, synchronous jerks most often affecting the neck, shoulders, upper arms, body, and upper legs. Consciousness does not usually seem to be impaired, although this is difficult to verify given the brief duration of <1 second; if several occur in rhythmic succession, this may be termed a clonic seizure, and may be associated with altered awareness. EEG during a myoclonic seizure typically shows a polyspike-and-slow-wave discharge. Myoclonic seizures occur in a variety of epilepsy syndromes. Rarely they may be seen as part of a progressive, degenerative condition (i.e., progressive myoclonic epilepsy).
Myoclonic Seizures

Generalized polyspike-slow-wave discharges
Atonic and tonic seizures, like atypical absence, are most common in people with other neurologic abnormalities in addition to epilepsy.

**Tonic seizures**
- are generalized (unlike partial motor seizures), involving bilateral musculature in a symmetric or nearly symmetric manner.
- characterized by flexion at the waist and neck, abduction and flexion or extension of the upper extremities, and flexion or extension of the lower extremities.
- typically occur during sleep
- last 2-20 seconds.
- EEG usually shows generalized, low-voltage, fast polyspikes.

**Atonic seizures**
- consist of a sudden loss of postural tone, often resulting in falls, or, when milder, head nods or jaw drops.
- consciousness is usually impaired and significant injury may occur.
- duration is usually several seconds, rarely more than 1 minute.
- EEG often shows an electrodecremental response.

Epileptic drop attacks may occur not just with atonic seizures, but also with myoclonic or tonic seizures if the legs are involved.
Tonic and Atonic Seizures
Primary generalized tonic-clonic (also called grand mal or convulsive seizures) seizures:
- cause loss of consciousness associated with an initial tonic phase of stiffening, a fall, and often a cry evoked by air forced through contracted vocal cords. Legs are usually extended, and arms may be extended, flexed, or each in succession.
- the subsequent clonic phase consists of jerking of the extremities which gradually slows before stopping.
- tonic-clonic seizures usually last 30-120 seconds.
- there may be drooling or foaming (resulting from lack of swallowing and excessive salivation); biting of the tongue, cheek, or lip, causing bleeding; and bladder or bowel incontinence.
- postictal lethargy and confusion often last minutes to hours, and may be followed by transient agitation.

EEG shows generalized polyspikes during seizures, but these are usually obscured by muscle artifact. Postictally, there is background suppression and then diffuse slowing.
Epilepsy is an umbrella term, under which many types of diseases and syndromes are included. Some authors distinguish between epilepsies and epileptic syndromes, depending on whether seizures are the only neurologic disorder (an epilepsy) or are one of a group of symptoms (an epileptic syndrome). Some of the epilepsies (e.g., juvenile myoclonic epilepsy) have well-defined genetics, clinical courses, and responses to medication. Others (e.g., temporal lobe epilepsy) have natural histories which are highly variable, and which reflect differences in pathology as well as in host response to that pathologic process and to the treatments administered.
The current classification of the epilepsies and epileptic syndromes attempts to separate these disorders according to their putative brain origins, that is, whether they arise in a circumscribed portion of the brain (partial), or appear to begin diffusely in the cortex and its deeper connections (generalized). The syndrome is idiopathic when the disorder is not associated with other neurologic or neuropsychologic abnormalities; symptomatic indicates that such an abnormality is present and the cause is known. Cryptogenic refers to syndromes that are presumed to be symptomatic but the cause in a specific patient is unknown. Many idiopathic epilepsies occur in children and adolescents, and often remit in adolescence or adulthood. There is evidence that most or all of these syndromes have a genetic basis, and that when this basis becomes known, they will move from the idiopathic to the symptomatic category.

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INTERNATIONAL CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES

1. Localization-Related (Local, Focal, Partial) Epilepsies and Syndromes

1.1 Idiopathic (with age-related onset)
   - Benign childhood epilepsy with centrotemporal spikes (‘rolandic epilepsy’)
   - Childhood epilepsy with occipital paroxysms

1.2 Symptomatic
   - Chronic progressive epilepsia partialis continua of childhood (e.g., ‘Rasmussen’s encephalitis’)
   - Frontal lobe epilepsies
   - Occipital lobe epilepsies
   - Parietal lobe epilepsies
   - Temporal lobe epilepsies

1.3 Cryptogenic

2. Generalized Epilepsies and Syndromes

2.1 Idiopathic (with age-related onset)
   - Benign neonatal familial convulsions
   - Benign neonatal convulsions
   - Benign myoclonic epilepsy in childhood
   - Childhood absence epilepsy (pyknolepsy)
   - Juvenile absence epilepsy
   - Juvenile myoclonic epilepsy

2.2 Cryptogenic or Symptomatic
   - West syndrome
   - Lennox-Gastaut syndrome

3. Epilepsies and Syndromes Undetermined Whether Focal or Generalized

4. Special Syndromes
Etiology of Seizures and Epilepsy

- Infancy and childhood
  - Prenatal or birth injury
  - Inborn error of metabolism
  - Congenital malformation

- Childhood and adolescence
  - Idiopathic/genetic syndrome
  - CNS infection
  - Trauma
Etiology of Seizures and Epilepsy

- Adolescence and young adult
  - Head trauma
  - Drug intoxication and withdrawal *
- Older adult
  - Stroke
  - Brain tumor
  - Acute metabolic disturbances *
  - Neurodegenerative

*causes of acute symptomatic seizures, not epilepsy
The initial evaluation after a single seizure should: 1) determine whether a seizure actually occurred, or whether the patient experienced some other transient event; 2) search for evidence of partial onset; 3) search for evidence of underlying central nervous system dysfunction; 4) search for evidence of systemic or metabolic disorders that could have precipitated the seizure; 5) attempt to classify the patient’s seizure and condition; 6) determine what diagnostic studies are appropriate; and 7) determine whether drug therapy should be instituted, and if so, with what agent.
Often, the patient is amnestic for the events surrounding the seizure, and the description must be obtained from relatives, friends, or bystanders. Observers may report behavior consistent with a complex partial seizure immediately preceding a convulsion. In other cases, the patient may recall localized motor activity, suggesting a simple partial motor seizure before losing consciousness. At times, the only evidence of partial onset may be a brief subjective event consistent with an aura; in this case it is important to determine whether the identical aura ever occurred before.

The examination of the patient who has experienced a seizure is often most revealing when conducted as soon after the seizure as possible, and should be frequently repeated to determine whether or not any observed deficits are transient. Post-ictal weakness, aphasia, or sensory dysfunction provide powerful lateralizing and sometimes localizing information. Upper motor neuron signs which are briefly present post-ictally (e.g., a transient unilateral Babinski sign) also provide important data. Signs which are not transient may indicate a pre-existing structural lesion (e.g., tumor) or a new condition (e.g., stroke), and may lead to the diagnosis of an acute symptomatic seizure, that is, a seizure resulting from a new brain insult, which does not necessarily imply the existence of epilepsy (although epilepsy may later develop).

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There are no pathognomonic physical signs proving that an event was a seizure, but there are many useful associations. Bites on the side of the tongue or cheek, and urinary and/or fecal incontinence, are more common after seizures than after loss of consciousness from other causes. The general physical examination is otherwise most useful when it uncovers evidence of a precipitant for an acute symptomatic seizure (e.g., meningitis), or of a genetic predisposition to seizures, such as a neurocutaneous syndrome (e.g., tuberous sclerosis).

The laboratory evaluation of a patient after a single seizure depends on the circumstances surrounding the event. Blood tests should be tailored to the patient’s age and clinical circumstances. Routine blood tests can indicate problems such as hypo- or hyperglycemia; sodium, calcium or magnesium deficiency; compromised cardiorespiratory, liver or kidney function; or infection. Any suspicion of meningitis or encephalitis mandates lumbar puncture (after assessing potential for brain herniation), but otherwise this procedure is generally not necessary. Because many illicit drugs can cause seizures, toxic screens of blood and/or urine should be performed, especially in adolescents and young adults.

Patients who have had a new-onset seizure should undergo an electroencephalogram (EEG) and, with certain definable exceptions, magnetic resonance imaging (MRI). A CT scan is useful if an acute process is suspected (e.g., intracerebral hemorrhage), but is inadequate to exclude small tumors or vascular malformations, hippocampal atrophy, and cortical dysplasia. Some common exceptions to the need for neuroimaging are children with uncomplicated febrile convulsions or with firm clinical and EEG findings consistent with well-defined idiopathic syndromes such as childhood absence epilepsy or benign epilepsy with centrotemporal spikes.
One or more precipitating factors can contribute to the patient’s seizure. The discovery of a precipitant does not obviate the need to search for intracranial pathology or a genetic predisposition toward seizures, but may lead to a non-epilepsy diagnosis (e.g., alcohol withdrawal seizure), and is very useful in counseling the patient. Common precipitants include metabolic and electrolyte imbalance (such as low blood glucose, low sodium, low calcium or low magnesium), antiepileptic medication reduction or inadequate AED treatment, hormonal variations, stress, infection, severe sleep deprivation, withdrawal from alcohol or other sedative agents, and administration of drugs with proconvulsant properties, such as central nervous system stimulants including cocaine, anticholinergics (including over-the-counter antihistamines), almost all dopamine blocking agents, newer antipsychotics (particularly clozapine), antidepressants (especially buproprion), immune suppressants such as cyclosporine, and antibiotics such as quinolones or imipenem-cilastatin.
Seizure Precipitants (cont.)

Metabolic and Electrolyte Imbalance

- Low blood glucose
  (or high glucose, esp. w/ hyperosmolar state)
- Low sodium
- Low calcium
- Low magnesium
# Metabolic abnormalities and seizures

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Hyponatremia</td>
<td>Osmotic shifts, disrupted ionic balance, In anoxia w/ shutdown of Na-K pump</td>
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<tr>
<td>Hypo- or hyperkalemia</td>
<td>Rare to cause seizure. Sometimes through hypomagnesemia</td>
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<tr>
<td>Hypo- or hypercalcemia</td>
<td>Usually other seizures first, such as tetany or altered consciousness</td>
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<tr>
<td>Hypoglycemia</td>
<td>BS &lt;50, disrupted Na/K pump</td>
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<tr>
<td>Hyperthyroidism</td>
<td>May exacerbate epilepsy but rarely is de novo cause</td>
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BS = blood sugar.
Seizure Precipitants (cont.)

Stimulants/Other Pro-convulsant Intoxication

- IV drug use
- Cocaine
- Ephedrine
- Other herbal remedies
- Medication reduction
Seizure Precipitants (cont.)

Medications that can lower seizure threshold

- Antidepressants
  - Bupropion
  - Tricyclics
- Neuroleptics
  - Phenothiazines
  - Clozapine
- Theophylline

- Isoniazid
- Penicillin
- Cyclosporin
- Meperidine
The EEG is most useful for classifying the seizure type and, in many cases, the epilepsy syndrome. A normal EEG does not exclude the diagnosis of epilepsy. The EEG is only a very brief time sample of the patient’s brain electrical activity and will miss intermittent or transient abnormalities. In evaluating a patient suspected to have had a seizure, an EEG showing interictal (between seizures) epileptiform activity provides corroborating evidence, but is not proof, unless the patient has a seizure during the EEG (in which case the epileptiform activity is ictal rather than interictal).

Epileptiform activity includes spikes, sharp waves, electrographic seizures, and some other stereotyped phenomena which are strongly associated with seizures. Spikes and sharp waves are interictal epileptiform events. Background abnormalities indicate localized or diffuse cerebral dysfunction, and may reflect a transient postictal disturbance or the underlying process responsible for the seizure.
EEG Abnormalities

Interictal left temporal sharp wave consistent with a diagnosis of partial epilepsy of left temporal origin.
EEG Abnormalities

*Interictal generalized polyspike-wave complex consistent with a diagnosis of idiopathic generalized epilepsy*
Whether therapy with antiepileptic drugs (AEDs) should be initiated after a first seizure is controversial. Within 5 years after a single, unprovoked seizure, 16–62% of patients have another seizure. Recurrence is more likely if there has been an earlier neurologic injury sufficient to cause seizures; a structural abnormality on neuroimaging; an abnormal, particularly epileptiform, EEG; or a family history of epilepsy. Most studies also suggest that partial (including secondarily generalized) seizures are more likely to recur than primarily generalized tonic-clonic seizures. Treatment can reduce (perhaps by 50%) but not eliminate the risk of a second seizure. The treatment decision must be made individually for each patient, considering the potential physical, psychological, and vocational consequences of further seizures and of AED therapy.
Before treatment is instituted, the clinician must decide whether the patient’s seizures are partial or generalized in onset. The drug of choice should have the best efficacy (ability to stop seizures) and lowest likelihood of adverse effects. Several comparison studies have shown minimal differences in efficacy of the standard AEDs. Thus, differences in expected adverse effect profile, and pharmacokinetic profile, as well as expense, should guide AED choice. Most patients can be optimally managed on a single AED. One must be sure that a given drug has failed before moving on to an alternative drug or a two-drug combination. If the patient has persistent seizures but no adverse effects, the dose can be increased as tolerated or until seizure control is obtained. The “therapeutic range” of serum concentrations is only a guideline—the patient’s clinical state determines the appropriate dose.
Most epilepsy patients are best managed with a single drug. **Monotherapy** can simplify treatment regimens, reduce adverse effects, and often improve seizure control. Only after one or more attempts to achieve a simplified regimen should one conclude that a given patient requires polytherapy. Patients on multiple AEDs should be considered for conversion to monotherapy, because even those with uncontrolled seizures may have equivalent or improved seizure control as well as fewer adverse effects by using high doses of a single AED rather than drug combinations. The clinician should first determine whether the patient has had an adequate trial of a first-line agent—i.e., whether seizures persisted even when the AED was gradually increased until troublesome adverse effects developed. When converting patients to monotherapy, one should try to first eliminate more sedating drugs (barbiturates and benzodiazepines). These should be withdrawn slowly, usually over several months. Though monotherapy is preferred, some patients with epilepsy require polytherapy.
AED Choice: More Considerations

- Limited placebo-controlled trials available, particularly of newer AEDs
- Several drugs are commonly used for indications other than those for which they are officially approved/recommended
- Choice of AED for **partial epilepsy**:
  - drug side effect profile and patient’s preference/concerns
- Choice of AED for **generalized epilepsy**:
  - predominant seizure type(s)
  - drug side-effect profile and patient’s preference/concerns

See appendix for ILAE Summary Guidelines and Summary of AAN evidence-based guidelines
Antiepileptic drugs can be roughly classified as broad-spectrum or partial agents. Broad-spectrum agents are useful in the treatment of both primary generalized seizures and partial-onset seizures. Partial agents are used for the treatment of partial-onset seizures but are generally avoided in primary generalized epilepsy as they can potentially exacerbate some seizure types (e.g., atypical absence seizures). Phenytoin and carbamazepine are sometimes used for primary generalized tonic-clonic seizures.
In partial onset seizures with secondary generalization, carbamazepine, phenytoin, valproate, phenobarbital, and primidone are usually effective. In partial seizures without generalization, phenytoin and carbamazepine may be slightly more effective. These conclusions are based on direct randomized comparison studies of these medications. Felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, rufinamide, lacosamide, ezogabine and perampanel are newer antiepileptic drugs approved by the FDA since 1993, and several new AEDs are likely to be approved within the next few years. After randomized clinical trials, all of these drugs received FDA approval for adjunctive treatment in patients with partial onset seizures. Of the new AEDs, only oxcarbazepine has FDA approval for monotherapy in new-onset partial seizures. Lamotrigine, topiramate and gabapentin are not FDA approved for first-line monotherapy but have demonstrated efficacy similar to that of immediate release carbamazepine in head-to-head trials and are recommended for this indication by the AAN. The FDA has approved lamotrigine as monotherapy in adults with partial seizures after failure of an enzyme-inducing AED such as phenytoin or carbamazepine. Levetiracetam is not FDA approved or in the AAN recommendations for new-onset partial seizures, but was demonstrated to have efficacy similar to carbamazepine in one comparative trial after the publication of the AAN guidelines. In practice,
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much of the choice of anti-epileptic drugs for partial seizures depends on the side-effect profile of the drug and the patient’s individual concerns.
Azar and Abou-Khalil, Seminars in Neurology, 2008 28:305-316

The Glauser et al. article also looked at the evidence for initial monotherapy in children and elderly adults.

In children, the best evidence exists for oxcarbazepine. There is evidence in support of carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin, although weaker than for oxcarbazepine. Clobazam, clonazepam, lamotrigine and zonisamide have some evidence for efficacy in monotherapy, but less than the previous group.

In the elderly, there is good evidence supporting initial monotherapy with gabapentin and lamotrigine, with a weaker level of evidence for carbamazepine, and some evidence for the potential efficacy of topiramate and valproate.
FDA Approved Indication for treatment of partial seizures:
Adjunctive only: Tiagabine, Levetiracetam, Vigabatrin, Lacosamide, Zonisamide, Gabapentin, Pregabalin
Monotherapy and adjunctive: Valproate, Phenytoin, Felbamate, Lamotrigine, Phenobarbital, Carbamazepine, Topiramate, Oxcarbazepine
In patients with generalized-onset seizures, the AED choice depends on the specific epileptic syndrome, and particularly the different types of generalized seizures associated. In generalized epilepsies characterized by tonic-clonic seizures, myoclonic seizures, and/or absence seizures, or in photosensitive epilepsy, valproate is usually considered the drug of choice. Clonazepam and phenobarbital or primidone can be useful in generalized seizures but often have greater sedative and behavioral effects than other AEDs. Clonazepam, a benzodiazepine, may lose some of its effectiveness after six months or less, due to the development of tolerance. Lamotrigine, topiramate, and zonisamide may be effective against some primarily generalized seizures, such as tonic-clonic, absence, and tonic seizures. Topiramate recently received an FDA indication as first line treatment of generalized tonic-clonic seizures. Phenytoin and carbamazepine, are effective for tonic-clonic but not for other types of generalized seizures. Carbamazepine may exacerbate some generalized-onset seizures including absence and myoclonic seizures. Lamotrigine may also worsen myoclonic seizures. This underscores the need for seizure classification for appropriate AED selection.

FDA Approval:
Adjunctive only: Levetiracetam, Lamotrigine
Both: Valproate, Phenytoin, Carbamazepine, Topiramate
In children with only absence seizures (no tonic-clonic seizures), ethosuximide and valproate are equally effective. Valproate has the advantage of protecting against the tonic-clonic seizures which may develop later; because of the risk of rare but potentially fatal valproate-induced hepatotoxicity, however, ethosuximide is considered safer. This valproate risk is maximal in children under age 2 years, especially those under age 6 months or with congenital metabolic disorders, who are treated with multiple AEDs. Valproate should also be used with caution in girls given its association with polycystic ovarian syndrome and teratogenicity.
AED Choice: Myoclonic Seizures

Best evidence:
- **Valproate**
- Levetiracetam (FDA indication as adjunctive tx)
- Clonazepam (FDA indication)

Possibly effective:
- Zonisamide, topiramate

May Precipitate or Aggravate:
- Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, vigabatrin, and possibly lamotrigine (in JME)
AED Choice: Lennox-Gastaut Syndrome

Best evidence/FDA indication*:  
- Topiramate, felbamate, clonazepam, lamotrigine, rufinamide, valproate, clobazam  
* FDA approval is for adjunctive treatment for all except clonazepam

Some evidence of efficacy:  
- Zonisamide, levetiracetam
### AED Mechanisms of Action

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<tr>
<th>AED</th>
<th>Na⁺ Channel Blockade</th>
<th>Ca²⁺ Channel Blockade</th>
<th>H-current Enhancement</th>
<th>Glutamate Receptor Antagonism</th>
<th>GABA Enhancement</th>
<th>Carbonic Anhydrase Inhibition</th>
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<tr>
<td>PHT</td>
<td>X</td>
<td>X (NMDA receptor)</td>
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<tr>
<td>CBZ, VPA</td>
<td>X</td>
<td></td>
<td>X (GABA_A)</td>
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<td>carb. benz.</td>
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<td>EPM</td>
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<tr>
<td>VPA</td>
<td>X</td>
<td>X</td>
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<tr>
<td>FBM</td>
<td>X</td>
<td>X</td>
<td>X (NMDA)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GBP</td>
<td>X</td>
<td>X</td>
<td>X (NMDA, glycine)</td>
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<tr>
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<td>X (lactate)</td>
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<tr>
<td>TPM</td>
<td>X</td>
<td>X</td>
<td>X (AMP, kainate)</td>
<td>X</td>
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<td></td>
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<tr>
<td>TGB</td>
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<td>LEV</td>
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<td>X (lactate)</td>
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<td>ZNS</td>
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<td>PGB</td>
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<tr>
<td>LCM</td>
<td>X (slow inact.)</td>
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<tr>
<td>VGB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X (metast.)</td>
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</tr>
</tbody>
</table>

Modified from White HS and Rho JB, Mechanism of Action of AEDs, 2010.

For more details: please see the Neuropharmacology Slide Section.
Antiepileptic drugs (AEDs) that are highly bound to serum proteins (e.g., phenytoin, valproate, and tiagabine) may be displaced from binding sites by other highly protein bound drugs (e.g., aspirin, warfarin, phenothiazines). In these cases, the serum concentration may not accurately reflect the unbound proportion of drug. Unbound (free) serum concentrations can be helpful in patients taking these drugs with other highly protein bound drugs, or in patients with significant renal disease or hypoalbuminemia.

Most AEDs are metabolized by hepatic enzymes, and may either induce or inhibit hepatic metabolism of other drugs. The exceptions are gabapentin and levetiracetam which have no measurable hepatic metabolism. Induction of hepatic enzymes by AEDs such as carbamazepine, phenytoin and phenobarbital may cause increased metabolism and decreased serum concentrations of many other drugs, such as steroid hormones (i.e., oral contraceptives) or warfarin. Felbamate and valproate are metabolic inhibitors and can increase serum concentrations of other hepatically metabolized drugs. Conversely, other drugs (e.g., erythromycin or fluoxetine, potent inhibitors) may inhibit the metabolism of AEDs. It is sometimes difficult to predict what type of interaction will occur when two AEDs or an AED and another drug are used together.
# AED Interactions: Anticoagulation

<table>
<thead>
<tr>
<th>AED</th>
<th>Antiplatelet/Anticoagulant</th>
<th>Potential Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin (PHT)</td>
<td>1. Warfarin</td>
<td>1. Increases INR*</td>
</tr>
<tr>
<td></td>
<td>2. Aspirin</td>
<td>2. Increases free PHT</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>Warfarin</td>
<td>Decreases INR</td>
</tr>
<tr>
<td>Phenobarbital (Pb)</td>
<td>Warfarin</td>
<td>Decreases INR</td>
</tr>
<tr>
<td>Primidone (PRM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid (VPA)</td>
<td>1. Warfarin</td>
<td>1. Slight decrease in INR</td>
</tr>
<tr>
<td></td>
<td>2. Aspirin</td>
<td>2. Increases free VPA</td>
</tr>
</tbody>
</table>

*AFDs increase metabolism of warfarin, but warfarin is 98% protein bound, and PHT and VPA increase warfarin’s free fraction. INR = international normalized ratio.


American Epilepsy Society 2015
Several AEDs are enzyme inducing drugs that can interfere with the efficacy of hormonal contraception. This includes combined oral contraceptive pills, progesterone only pills, the estrogen patch, the vaginal ring, the etonogestrol implant (Nexplanon). The enzyme inducing effects of topiramate, oxcarbazepine and felbamate may be dose related and topiramate is only known to effect the synthetic estrogen metabolism. Never-the-less, the CDC advises against combining these drugs with hormonal contraception and recommends an IUD as the contraceptive of choice. Depo-medroxyprogesterone may still be efficacious in some scenarios, but the dose may need to be increased to achieve amenorrhea.
Lamotrigine is cleared by glucuronidation, a process induced by estrogen, particularly synthetic estrogens. A woman taking lamotrigine will likely experience a significant drop in her AED levels and possible increase in seizure frequency if estrogen containing hormonal contraception is started without dose adjustment. Oxcarbazepine and valproic acid are also cleared by glucuronidation and it is possible they may be affected similarly though this has not been shown as clearly.

The CDC recommends an IUD as the contraceptive method of choice for women taking lamotrigine due to the effect of synthetic estrogen on lamotrigine levels. It does not restrict use of progesterone only methods, however Lamotrigine has also been shown to decrease the AUC and Cmax of levonorgestrel, a synthetic progestin in many forms of hormonal contraception. In one study oral contraceptive pills and lamotrigine ovulation did not occur despite this decrease but more spotting was seen. This should be kept in mind if prescribing hormonal contraception to women taking lamotrigine.
The “therapeutic range” of AED serum concentrations are those that are often associated with seizure control without significant toxicity, and have been derived from population studies. This range is a useful guide, but cannot substitute for assessing the individual patient’s clinical response to an AED. Many patients can experience excellent seizure control and no adverse effects with serum concentrations above or below the therapeutic range. Furthermore, some patients experience troublesome side effects with levels within or even below this range. Clinicians should not rigidly adhere to a therapeutic AED range but rather use serum concentrations to aid in balancing AED efficacy and toxicity.

Pharmacokinetic factors should also be considered when interpreting AED serum concentrations. Most drugs need five half-lives to reach steady state. Drugs with long half-lives, such as phenytoin, phenobarbital, and zonisamide may require two weeks or more to reach steady-state. Thus, serum concentrations drawn too soon after drug initiation or dose change may not accurately reflect the steady-state. Conversely, serum concentrations of drugs with short half-lives may be significantly affected by the time interval between the last dose and the serum sample.
AEDs: Common Adverse Effects

Typically dose-related:

- Dizziness, Fatigue, Ataxia, Diplopia
  - all AEDs
- Irritability, neuropsychiatric side effects
  - Levetiracetam, ezogabine
- Word-finding difficulty
  - Topiramate
- Weight loss/anorexia
  - Topiramate, zonisamide, felbamate
- Weight gain
  - Valproate (also associated with polycystic ovarian syndrome)
  - Carbamazepine, gabapentin, pregabalin
AEDs: Serious Adverse Effects

Typically Idiosyncratic:

- Renal stones
  - Topiramate, zonisamide
- Anhydrosis, heat stroke
  - Topiramate, Zonisamide
- Acute closed-angle glaucoma
  - Topiramate
- Hyponatremia
  - Carbamazepine, oxcarbazepine
- Urinary Retention
  - Ezogabine
AEDs: Serious Adverse Effects

Typically Idiosyncratic:

Aplastic anemia
  • Felbamate, zonisamide, valproate, carbamazepine

Hepatic Failure
  • Valproate, felbamate, lamotrigine, phenobarbital

Peripheral vision loss
  • Vigabatrin

Rash
  • Phenytoin, lamotrigine, zonisamide, carbamazepine
AEDs: Adverse Effects - Rash

- 15.9% patients experienced a rash attributed to an AED

- Average rate of AED-related rash for a given AED 2.8%, 2.1% causing AED discontinuation.

- Predictors significant in multivariate analysis:
  - occurrence of another AED-rash


American Epilepsy Society, 2015
AED Adverse Effects - Rash

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TENS)

- Severe life threatening allergic reaction
- Blisters and erosions of the skin, particularly palms/soles and mucous membranes
- Fever and malaise
- Rare: severe risk roughly 1-10/10,000 for many AEDs
  - *Rapid titration of lamotrigine especially in combination with valproate increases risk*
AED-related rash in adult patients with epilepsy

Average incidence of rash = 2.8%

Antiepileptic Drug (n)

▲▲ = rash rate significantly greater than average of all other AEDs (p<0.001)
▼▼ = rash rate significantly lower than average of all other AEDs (p<0.003)
▲ = trend towards significantly higher than average rash rate of all other AEDs (0.003>p>0.05)
▼ = trend towards significantly lower than average rash rate of all other AEDs (0.003>p>0.05)

American Epilepsy Society, 2015
AEDs: Adverse Effects - Rash

Drugs *rarely* associated with rash

- Valproate
- Gabapentin
- Pregabalin
- Levetiracetam
- Topiramate
AED-related rash in Asian patients

- FDA alert 12/2007: Risk of "dangerous or even fatal skin reactions" such as Steven-Johnson Syndrome and Toxic epidermal necrolysis is increased in patients with HLA-B*1502 allele
  - Estimated absolute risk for those with the allele: 5%
- This allele is almost exclusively found in Asians:
  - 10-15% of population in China, Thailand, Malaysia, Indonesia, Philippines and Taiwan
  - 2-4% in India
  - <1% in Japan and Korea
- 59/60 Asian patients w/ SJS/TEN had this allele vs 4% of CDZ tolerant patients
- Asians "should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine"
- These patients may also be at risk with other AEDs (phenytoin, oxcarbazepine, lamotrigine)

www.fda.gov
Possible suicide risk with AEDs

Recent FDA alert (1/2008):
- Meta-analysis of 199 placebo-controlled add-on tx trials
  (44,000 patients)
- Suicidality with adjunct AEDs than adjunct placebo:
  - 0.43% vs 0.22%
- Extra 2.1 patients per 1000 more patients will have suicidality
- 4 suicides with AEDs vs 0 with placebo
  “generally consistent across the 11 AEDs”

Data analysis is controversial and overall difference is very small

Further investigation is needed

Clinicians should be aware of potential risk and screen for depression/suicidality

www.fda.gov
Before starting an AED, the patient should be informed about adverse effects and the realistic probability of efficacy. For example, fewer than 50% of adults with partial-onset seizures remain seizure-free for more than 12 months after starting first-line monotherapy. Patients should record seizure frequency and type and adverse effects on a calendar, so that efficacy can be quantitated and compared among AEDs. Potential provocative factors such as menses can also be charted. Most AEDs should be introduced slowly to minimize adverse effects.

In addition, before starting AEDs, and at intervals during the first months of use, it is reasonable to check CBC, electrolytes, liver function tests, and serum drug concentrations.
Antiepileptic drugs can eventually be withdrawn successfully in more than 60% of patients who remain free of seizures. Most neurologists require patients to be seizure free for 2 to 4 years before discontinuing AEDs, and the drugs are generally discontinued over a 2 to 6 month period. The underlying epileptic syndrome also may influence the success of antiepileptic drug withdrawal. For example, the success rate for drug discontinuation in juvenile myoclonic epilepsy is only about 20%, whereas in benign epilepsy with centrotemporal spikes, it is nearly 100%. The best prognosis for eventual withdrawal of AEDs is in patients with idiopathic generalized epilepsy (but not juvenile myoclonic epilepsy), a normal neurologic exam, and no structural brain lesion; even with these favorable factors, however, there is never a guarantee of remaining seizure free.
When a seizure recurs, the major issues to consider include: 1) whether this is a manifestation of progressive pathology, such as a tumor or a neurodegenerative disorder; 2) whether there was a precipitant which could be avoided in the future; 3) if the patient was receiving an AED, a) whether compliance or some other pharmacokinetic factor (i.e. absorption, metabolism) is at issue, or b) whether the dose or the medication should be altered; and 4) if the patient was not taking medication, whether this recurrent seizure is an indication to institute treatment.

In general, patients with partial seizures (with or without secondary generalization) who experience a change in seizure pattern, especially a change in the initial manifestation, should be evaluated for a progressive lesion with a neurologic exam, and possibly a repeat MRI and EEG.

For patients receiving AEDs, a recurrent seizure may be an indication to obtain a serum concentration of the drug. This is especially true of a patient whose seizures have been under good control for some period of time. If the serum concentration of an AED has fallen, one must determine the cause of the fall and attempt to re-establish the previously effective level (i.e. non-compliance, pharmacokinetic interaction). Conversely, if the patient has frequent seizures with serum concentrations in the “therapeutic” range, further measurements may not be useful and a change in management strategy may be indicated.
Medical Comorbidities of Epilepsy

- Most medical conditions occur with increased incidence in patients with epilepsy compared to patients without it.
- Some of these may be pathophysiologically related (stroke) and some may be less so.
- Recurrent seizures may be feature of a cryptogenic condition that has myriad downstream manifestations (?auto-immune illness).
<table>
<thead>
<tr>
<th>Condition</th>
<th>No Epilepsy %</th>
<th>Any Epilepsy %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IICart</td>
<td>11.3</td>
<td>18.3</td>
</tr>
<tr>
<td>HTN</td>
<td>29</td>
<td>34</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.4</td>
<td>4.3</td>
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<tr>
<td>Arthritis</td>
<td>21.4</td>
<td>30.9</td>
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<td>Face Pain</td>
<td>4.8</td>
<td>14.2</td>
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<tr>
<td>HA/Migraine</td>
<td>16.2</td>
<td>34.7</td>
</tr>
<tr>
<td>Ulcer</td>
<td>28.9</td>
<td>47.1</td>
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Psychiatric Comorbidities of Epilepsy

- Anxiety
  - Generalized Anxiety Disorder
  - Panic Attacks

- Affective
  - Unipolar Depression
  - Bipolar Disorder

- Psychosis
  - Post-ictal
  - Chronic Interictal/Schizophrenia-like
Anxiety and Epilepsy

- With rigorous diagnostic criteria prevalence of anxiety disorders in epilepsy patients in the community are between 14.8 - 25% (Edoh '87 and Jacoby '96)
- Pariente in 1991 reported an incidence of 21% of panic attacks in French Epilepsy patients compared to 3% of controls
- Hospital based studies show similar rates as community (Perino '96, Gureje '91)
- In epilepsy surgery candidates rates have been found as high as 31% (Manchanda '96)
Affective Disorders and Epilepsy

- Major Depression
- Bipolar Disorder
- Subsyndromal Symptoms
Major Depression and Epilepsy

- Conservative estimates state that 20% of Epilepsy patients will develop Depression
- Some estimates as high as 50 - 80%
- Women with significantly higher rates
- Rates vary regionally
- Studies have consistently shown that Depression increases the risk of developing Epilepsy, suggesting a common stem etiology
Bipolar Disorder and Epilepsy

- Lifetime prevalence of Bipolar Disorder in Epilepsy patients is 1.5 - 2%
- Much less common than Depression
- Notably, post-ictal psychosis can have a bipolar flavor, schizophreniform but with preserved affect and mild hypomania
- Many AED’s are mood stabilizers, most notably: Lamictal, Depakote, Tegretol, Trileptal
Sub-Syndromal Symptoms

- The most common presentation of Affective Disorders in Epilepsy patients is sub-syndromal depression
- They don't meet criteria for Major Depressive Episode but can be significantly symptomatic
- Depressive symptoms have been shown to correlate with quality of life consistently, even when seizure frequency, type, etc. have not
Psychosis and Epilepsy

- Ictal
- Post Ictal
- Interictal
Ictal Psychosis

- Can range from a sense of being followed over the contralateral shoulder (amygdaloid focus) with mild paranoia to hallucinations of all sorts (auditory, visual, olfactory, tactile)
- Can be associated with EEG changes, though not frequently if awareness is unaltered
- Fluctuating awareness and paranoia/hallucinations with lability are hallmarks of non-convulsive status epilepticus
Post-Ictal Psychosis

- Often after a lucid period of 24 - 36 hours.
- Bizarre in nature often, religious at times, schizophreniform in content
- Affect often preserved with irritability or hypomania
- Can last hours to days to even weeks
- Treating with anti-psychotics for a few weeks limits intensity and duration
- RF include, prolonged seizures, seizures with l.o.c., bitemporal foci, clusters of seizures, GTC’s, family history of mood disorders, and longer duration of epilepsy
Interictal Psychosis

- Most commonly seen in Temporal Lobe Epilepsy of long duration with poor seizure control
- Post-ictal Psychoses increase in frequency and duration and then become chronic interictal psychosis without return to baseline
- Very schizophreniform looking with paranoid, bizarre, religious delusional systems
- Require chronic anti-psychotic pharmacologic and psychosocial interventions
- Can occur de novo after Epilepsy Surgery
Diagnosis of Psychiatric Symptoms in Epilepsy

- Every visit with a provider should include a discussion of psychiatric symptoms with patient and family
- Remember that sub-syndromal symptoms can significantly impact quality of life and respond to treatment
- Know when to refer to psychiatrist or therapist for ongoing treatment
- Depression and Anxiety should always be explored
- Screen for post-ictal psychosis
Psychosocial Concerns and Quality of Life in Epilepsy

- The most common concerns noted by patients with epilepsy:
  - Driving (70%)
  - Independence
  - Work and Education
  - Social Embarrassment
  - Medication Dependence
  - Mood/Stress
  - Safety

- Giliam and Kuzniecky 1997
Most cases of epilepsy are well controlled with AEDs, 20–30% of cases, however, are not. Surgical therapy is worth considering in patients in whom seizures and/or medication side effects significantly impair quality of life. Surgical treatment is indicated in such patients if seizures arise from an area that can be removed without causing unacceptable neurological deficits. Candidacy for surgery is determined by a constellation of tests including video/EEG monitoring, neuroimaging, and neuropsychometric studies. In some cases, palliative surgical procedures are performed to reduce seizure frequency or severity even though there is a low expectation of cure. These procedures typically involve disconnections, such as cutting the corpus callosum, rather than removing brain tissue.
Overall, the most important determinant of a successful surgical outcome is patient selection. This requires detailed pre-surgical evaluation to characterize seizure type, frequency, and site of onset; neuropsychological, psychiatric, and psychosocial functioning; and degree of disability.

History and physical examination are performed to determine, if possible, the etiology, course, and functional impact of the patient’s epilepsy. Details of ictal events can provide important localizing information, such as an autonomic or psychic-cognitive aura suggesting mesial temporal lobe origin. Adequacy of previous, unsuccessful AED trials should be assured.

Neuromaging techniques are very important to presurgical planning. MRI is necessary to identify potential symptomatic lesions (tumor, dysplasia) and mesial temporal sclerosis. Specific protocols enhance sensitivity of MRI (i.e. 1.5mm coronal cuts for mesial temporal sclerosis). Positron emission tomography (PET) and single photon emission computed tomography (SPECT) can also help identify functional abnormalities that can point to the epileptogenic zone. Magnetoencephalography (MEG) is a newer technique that uses the magnetic field of interictal activity to localize the epileptogenic focus. It also has applications to functional brain mapping.

Formal neuropsychological testing can reveal specific focal or multifocal cognitive deficits that can at times be correlated with the neuroimaging and EEG data. This testing may help localize an abnormally functioning brain area and also serve as a baseline for post-surgical evaluation.
Continued from Slide 84

Psychiatric and psychosocial evaluation are vital to assess current level of functioning and to ensure that the patient and family have realistic goals and attitudes. This assessment also establishes a relationship that may be helpful in dealing with complicated adjustment issues that may occur even after successful epilepsy surgery.

Sodium amobarbital injections during carotid angiography accompanied by language and memory testing (Wada test) reveal critical information regarding lateralization of language and memory, which is necessary to assess whether the patient can tolerate epilepsy surgery. Functional MRI is being used in some centers.
Temporal lobectomy is the most common surgical procedure for epilepsy and can be performed in either the dominant or non-dominant hemisphere without significant language impairment. Among highly selected patients, more than 80% (in some studies) are free of complex partial or secondarily generalized seizures following surgery, though many remain on medications. Extra-temporal resections, most commonly in the frontal lobe and less often in the parietal or occipital region. Extra-temporal resections are performed mainly in patients with structural lesions or developmental abnormalities and occasionally in cryptogenic focal epilepsies. Rare cases involving seizures arising from large parts of a cerebral hemisphere, associated with fixed hemispheric deficits, can be treated in children with an anatomic hemidecortication or functional hemispherectomy. These surgeries can be very successful for cases of hemimegalencephaly, Rasmussen’s syndrome, Sturge-Weber syndrome, and large cortical strokes. Palliative procedures such as corpus callosotomy may be performed in patients with intractable drop or atonic seizures as well as tonic-clonic and other generalized seizures.
Approximately two-thirds of patients with mesial temporal epilepsy become free of seizures, excepting aura, after anterior temporal lobectomy. There is only one class I randomized controlled study of epilepsy surgery outcomes (Wiebe et al. NEJM 2001). In this study of 80 patients with mesial temporal lobe epilepsy, 64% of those who received surgery were seizure free of all seizures excluding simple partial seizures, compared to 8% who received medical treatment. A meta-analysis of 24 class IV studies demonstrated similar results (see slide). In a metanalysis of Class IV series, these findings change little when data are examined with respect to geographic region, longer follow-up, and surgery after the advent of MRI (Engel, J et al. Neurology 2003). Other studies suggest that the presence of mesial temporal sclerosis on MRI and a history of febrile seizures are prognostic of a better outcome. If MRI and interictal EEG are concordant, the possibility of seizure freedom can be as high as 77% (Gilliam et al. Epilepsia 1997).

No class I or II data is available on extra-temporal or non-mesial temporal lobe resections. The data presented here is based on a Metanalysis of 14 Class IV series (Engel, J et al. Neurology 2003). In this study, approximately half of patients who undergo localized neocortical resections became free of disabling seizures, and 21% are unimproved. Neocortical resections encompass a much more heterogeneous group of surgeries and types of...
epilepsy. Outcomes probably vary greatly based on region of resection and etiology. In a subset of series that looked at patients with discrete lesions separately, 63% of 131 patient’s with lesions were seizure free.

Based on the above data the American Academy of Neurology, the American Epilepsy Society, and the American Academy of Neurological Surgeons concluded that anterior mesial resection should be considered in patients with disabling complex partial seizures who have failed appropriate trials of first-line antiepileptic drugs and meet established criteria for an anteromesial temporal lobe resection. In regard to localized neocortical resections, they concluded that there is insufficient evidence at this time to make a definitive recommendation as to whether patients will benefit or not benefit from surgical resection. (Engel 2003)
Epilepsy Surgery

Corpus Callosumotomy
- Palliative surgery for intractable epilepsies with drop attacks (i.e., Lennox-Gastaut Syndrome)
- Up to 75% have >75% reduction in atonic seizures
- Risk of disconnection syndromes

Hemispherectomy
- Indicated for catastrophic hemispheric epilepsies, usually presenting in children (i.e., Rasmussen’s encephalitis, hemimegalencephaly)
- 43-79% seizure free (varies by etiology)
- “Functional hemispherectomy” (disconnection without removal) now more commonly performed

Multiple Subpial Transections
- Cuts horizontal cortical-cortical connectives
- Generally reserved for epileptogenic regions in functional cortex


American Epilepsy Society 2015
The **vagus nerve stimulator** (VNS), a device that provides intermittent electrical stimulation of the vagus nerve, was shown in several studies to be effective in reducing the frequency of complex partial seizures, and received FDA approval in 1997. The stimulator is similar to a cardiac pacemaker and is surgically implanted subcutaneously. Intermittent stimulation is delivered every 0.3-10 minutes for 7-30 seconds, but patients who experience a seizure warning can trigger the device manually, with anecdotal success for some. The mechanism by which stimulation reduces seizures is not well established. Adverse effects include hoarseness, throat pain, or a feeling of dyspnea during stimulation; these are generally mild. Central nervous system side effects typical of AEDs are not present. The stimulator has been studied only in combination with AED treatment, but in this setting, efficacy against medication-resistant partial seizures was comparable to that of some of the new AEDs. The cost of the device and its implantation may be limiting factors. Clinical trials demonstrate that <5% of patients become seizure free with VNS placement but approximately 1/3 of patients experience a clinically significant decrease in their seizure frequency.

The FDA has approved the device for partial onset seizures, but it may have value for generalized epilepsies, especially Lennox Gastaut syndrome and specifically atonic seizures. Many centers will try a VNS prior to a callostomy for intractable atonic seizures. VNS has a responder rate of 40% (i.e. 40% of patients have a 50% or more decrease in their seizures). The VNS was approved in late 2005 for treatment-resistant depression by the FDA.
Although AEDs are the mainstay of treatment, alternative treatment modalities have varying degrees of clinical and experimental support. Lifestyle modifications, particularly avoidance of alcohol and sleep deprivation, can be very important in certain syndromes and individuals. Relaxation, biofeedback, and other behavioral techniques can help a subset of patients, especially those with a reliable aura preceding complex partial or secondarily generalized seizures. Dietary supplements are of unproven value, except for pyridoxine (vitamin B6), which is crucial for treating rare pyridoxine dependency of neonates and infants and for seizures due to antituberculous therapy with isoniazid. Herbal remedies are currently also under investigation.
The ketogenic diet has been used for more than 80 years in children with severe seizure disorders. It is based on the observation that ketosis and acidosis have anti-seizure effects, although recently glucose stabilization, caloric restriction, and direct anticonvulsant effects of polyunsaturated fatty acids have been reported in animal models. Because of risks of severe metabolic abnormalities during and after the initial fasting period, this diet is initiated in the hospital. Recently, the requirement for a fasting period has been shown to be not valid; most centers will individualize nowadays. Strict protein, calorie, and especially carbohydrate restriction in the setting of a high fat diet is needed for ketosis, and can be difficult to maintain. In 10% of patients with intractable epilepsy, staying on this diet for months or years can result in a sustained seizure freedom, and allow for withdrawal of AEDs. Side effects include weight loss, acidosis, kidney stones (5%), growth slowing, and dyslipidemia.
The recent emergence of less restrictive ketogenic diets, such as the modified Atkins diet from Johns Hopkins and the low-glycemic index treatment from Massachusetts General, have added to options for children as well as adults with intractable epilepsy. Both these diets have similar response rates (although in small series) to the traditional ketogenic diet with fewer side effects. Further clinical trials are underway.
Status epilepticus is defined as: 1) an episode of more than 5 minutes of continuous clinical or electrographic seizure activity, or 2) two or more sequential seizures spanning this period without full recovery between seizures.

Clinically most seizures last less than 5 minutes, and those persisting longer are unlikely to stop spontaneously. Therefore, one should initiate treatment for the seizures lasting longer than 5 minutes.

The incidence of status epilepticus is at least 60,000 cases/year in the U.S. with higher rates among the very young and very old. Status epilepticus is an emergency because of its morbidity and mortality, and any seizure type may manifest as status epilepticus. The outcome of convulsive status epilepticus largely depends on etiology, but prompt treatment can improve outcome.

From a practical standpoint, status epilepticus may be divided into convulsive and non-convulsive forms. The convulsive forms may be generalized or partial. The non-convulsive forms are difficult to classify on clinical grounds but are often divided electroencephalographically into absence status (in which the EEG demonstrates generalized spike-wave activity) and complex partial status (in which the EEG may show a variety of localized rhythmic discharges).
Status Epilepticus (SE)

- A medical emergency
  - Adverse consequences can include hypoxia, hypotension, acidosis, hyperthermia, rhabdomyolysis and neuronal injury
  - Know the recommended sequential protocol for treatment and distribute a written protocol to emergency rooms, ICUs and housestaff.
  - Goal: stop seizures as soon as possible
Mortality of SE by Age

% Mortality

Age Group (Years)

16-20  20-29  30-39  40-49  50-59  60-69  70-79  80+

70
60
50
40
30
20
10
0
Mortality of SE by duration

![Bar chart showing mortality of SE by duration in hours](chart.png)

Seizure Duration (Hours)

- 0:30-0:59
- 1:00-1:59
- 2-4
- 5-10
- 11-23
- 24+

% Mortality

- 0
- 10
- 20
- 30
- 40
- 50


American Epilepsy Society 2015
SE Treatment Algorithm

- Check emergency ABC’s
- Give O2
- Obtain IV access
- Begin EKG monitoring
- Check fingerstick glucose
- Draw blood for Chem-7, Magnesium, Calcium, Phosphate, CBC, LFTs, AED levels, ABG, troponin
- Toxicology screen (urine and blood).
- Thiamine 100 mg IV; 50 ml of D50 IV unless adequate glucose known.

# Status Epilepticus: First-line Treatment Options

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Route</th>
<th>Dosing</th>
<th>Maximum Dose</th>
<th>Class &amp; Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>LORAZEPAM</td>
<td>IV</td>
<td>0.1mg/kg</td>
<td>4mg @ 2mg/min May repeat x1 in 5-10 min</td>
<td>Class I Level A</td>
</tr>
<tr>
<td>MIDAZOLAM</td>
<td>IM Nasal</td>
<td>0.2mg/kg</td>
<td>10mg</td>
<td>Class I Level A</td>
</tr>
<tr>
<td></td>
<td>Buccal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIAZEPAM</td>
<td>PR</td>
<td>0.2mg/kg</td>
<td>20mg</td>
<td>Class IIa Level A</td>
</tr>
</tbody>
</table>

I Intervention is useful and effective. Treatment benefits clearly exceed risks

IIa Evidence/expert opinion suggest intervention is useful/effective. Treatment benefits exceed risk

IIb Strength of evidence/expert opinion about intervention usefulness/effectiveness is less well established. More data are needed; however, using this treatment when warranted is not unreasonable

III Intervention is not useful or effective and may be harmful. Benefit does not exceed risk

A Adequate evidence is available from multiple, large, randomized clinical trials or meta-analyses

B Limited evidence is available from less rigorous data, including fewer, smaller randomized trials, nonrandomized studies, and observational analyses

C Evidence relies on expert/consensus opinion, case reports, or standard of care
**I** Intervention is useful and effective. Treatment benefits clearly exceed risks

**IIa** Evidence/expert opinion suggest intervention is useful/effective.

**Treatment benefits exceed risk**

**IIb** Strength of evidence/expert opinion about intervention usefulness/effectiveness is less well established. More data are needed; however, using this treatment when warranted is not unreasonable

**III** Intervention is not useful or effective and may be harmful. Benefit does not exceed risk

<table>
<thead>
<tr>
<th>Infusions</th>
<th>Initial Dose</th>
<th>Continuous Infusion</th>
<th>Class &amp; Level of Evidence</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.2mg/kg @ 2mg/min</td>
<td>0.05-2mg/kg/hr</td>
<td>Class IIa Level B</td>
<td>Respiratory depression Hypotension</td>
</tr>
<tr>
<td>Propofol</td>
<td>1-2mg/kg @ 20mcg/kg/min</td>
<td>30-200 mcg/kg/min</td>
<td>Class IIb Level B</td>
<td>Respiratory Depression Hypotension Propofol infusion syndrome Renal Failure</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>5-15 mg/kg @ ≤ 50mg/min</td>
<td>0.5-5mg/kg/hr</td>
<td>Class IIb Level B</td>
<td>Respiratory depression Hypotension Cardiac depression Paralytic ileus Prolonged mental status depression</td>
</tr>
</tbody>
</table>

A Adequate evidence is available from multiple, large, randomized clinical trials or meta-analyses

B Limited evidence is available from less rigorous data, including fewer, smaller randomized trials, nonrandomized studies, and observational analyses

C Evidence relies on expert/consensus opinion, case reports, or standard of care
SE Treatment Algorithm

Begin EEG monitoring ASAP if patient does not rapidly awaken, or if any CIV treatment is used. ~20% of those patients successfully treated clinical for status will still be seizing on EEG.

A major problem for primary care physicians and neurologists is recognizing transient events that resemble seizures. Transient ischemic attacks, migraine, sleep disorders, movement disorders, and metabolic disturbances can produce episodes of altered mentation or movement. History, physical examination during or after attacks, and appropriate laboratory and radiologic studies can usually distinguish these events from epileptic seizures.
Differential Diagnosis of Non-epileptic Events: Psychogenic

- Psychogenic Seizures
- Malingering
- Panic Attacks
- Intermittent Explosive Disorder
- Breath-holding Spells
Syncope of vasovagal or cardiogenic origin can mimic epileptic attacks, especially when tonic extension of the trunk and limbs or several clonic jerks are observed, and lead incorrectly to the diagnosis of a seizure. Brief tonic posturing or clonic movements are common with syncope. Rarely, when the person is particularly susceptible or the ischemia is prolonged, a convulsion can result in convulsive syncope, which is a primary cardiovascular not cerebral disorder, and should not be treated as an epileptic seizure. Loss of consciousness exclusively in the standing or sitting position, painful stimuli or a very hot environment as provocative factors, and a prodrome of warmth, nausea, diaphoresis, and a gradual fading of binocular vision suggest syncope rather than seizures. A rapid return to normal mentation is also more characteristic of syncope than of seizures.
Clinical history can help distinguish between syncope and seizure. The features most suggestive of a generalized seizure are postictal lethargy and confusion (most useful), lateral tongue biting, frothing, cyanosis, and postictal diffuse myalgias.
### Syncope vs Seizure: During Spell

<table>
<thead>
<tr>
<th></th>
<th>Syncope</th>
<th>Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallor</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>&lt;20 secs</td>
<td>&gt;60 secs</td>
</tr>
</tbody>
</table>

Hirsch et al, Merritt’s Textbook of Neurology, 2007
## Syncope vs Seizure: During Spell

<table>
<thead>
<tr>
<th></th>
<th>Syncope</th>
<th>Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automatisms</td>
<td>Occasional</td>
<td>Common</td>
</tr>
<tr>
<td>Tongue biting, lateral</td>
<td>Rare</td>
<td>Occasional</td>
</tr>
<tr>
<td>Frothing/hyper-salivation</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

Hirsch et al, Merritt’s Textbook of Neurology, 2007
## Syncope vs Seizure: During Spell

<table>
<thead>
<tr>
<th></th>
<th>Syncope</th>
<th>Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movements</td>
<td>Few clonic or myoclonic jerks or brief tonic posturing</td>
<td>Prolonged tonic phase » rhythmic clonic mvmts</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt; 15 seconds</td>
<td>30 - 120 seconds</td>
</tr>
<tr>
<td>Frothing/hyper-salivation</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

Hirsch et al., Merritt’s Textbook of Neurology, 2007
## Syncope vs Seizure: After spell

<table>
<thead>
<tr>
<th></th>
<th>Syncope</th>
<th>Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion/ disorientation</td>
<td>Rare; &lt;30 secs</td>
<td>Common; several mins or longer</td>
</tr>
<tr>
<td>Diffuse myalgias</td>
<td>Rare, brief, usually shoulders/chest</td>
<td>Common, hours-days</td>
</tr>
<tr>
<td>Creatine kinase elevation</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

*Hirsch et al. Merritt’s Textbook of Neurology, 2007*
Features That Are Not Helpful in Differentiating Syncope from Seizure

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Incontinence</td>
<td>♦ Injury other than lateral tongue biting</td>
</tr>
<tr>
<td>♦ Prolactin level</td>
<td>♦ Eye movements (rolling back)</td>
</tr>
<tr>
<td>♦ Dizziness</td>
<td>♦ Brief automatisms</td>
</tr>
<tr>
<td>♦ Fear</td>
<td></td>
</tr>
</tbody>
</table>

Hirsch et al, Merritt’s Textbook of Neurology, 2007
Migraine and epilepsy are related disorders that share similar pathophysiological features. Approximately 6% of migraineurs have epilepsy (vs. 0.5% in the general population) and 24% of patients with epilepsy have migraine (Ottman & Lipman, Neurology 1996). It can be difficult to distinguish migraine from a partial seizure, particularly if they co-exist in the same patient. Migranous auras are most likely to be confused with occipital seizures in that they both may involve visual phenomenon. Migrane auras are longer in duration, typically are black and white, and should not be followed by a complex partial or generalized seizure. Both disorders may or may not involve headache, nausea and vomiting.

<table>
<thead>
<tr>
<th></th>
<th>Migraine</th>
<th>Occipital Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>5-20 min</td>
<td>0.5-5 min</td>
</tr>
<tr>
<td>Typical Content</td>
<td>B&amp;W; straight lines; slow spread</td>
<td>Color, round, variable spread</td>
</tr>
<tr>
<td>Laterality</td>
<td>Either side</td>
<td>Always same side (contralateral)</td>
</tr>
<tr>
<td>Associated Features</td>
<td>Altered awareness, automatisms</td>
<td></td>
</tr>
</tbody>
</table>
Psychogenic seizures are noted in 10-45% of patients evaluated at epilepsy centers. They can occur at any age after early childhood and are more common in women. Recognition allows avoidance of the intoxicating AED doses which are often used because seizures are refractory. One must maintain a high degree of suspicion when seizures are refractory to therapy or when atypical features are present. Because physicians generally rely on patient and witness accounts rather than direct observations of seizures, the chances for misdiagnosis are high. Diagnosis is best established by recording typical attacks with video-EEG. Limitations of this technique must be kept in mind, particularly susceptibility to movement and other artifacts, and potential false negatives during simple partial seizures and some frontal lobe seizures.

A detailed assessment of psychosocial stresses and underlying psychopathology is essential. In many cases, the underlying stressor can be identified (e.g. history of physical or sexual abuse). A significant proportion (10-40%) of patients with psychogenic NES also have epilepsy, an extremely challenging situation for both diagnosis and therapy.
Psychogenic Non-epileptic Seizures

FEATURES SUGGESTIVE OF NONEPILEPTIC PSYCHOGENIC SEIZURES

- Eye Closure
- Pelvic thrusting
- Opisthotonos
- Side-to-side head shaking
- Prolonged duration (>4 minutes)
- Stopping and starting
- Suggestibility

See next page for

TABLE 7. ICTAL FEATURES SUGGESTING NONEPILEPTIC PSYCHOGENIC SEIZURES
<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Caveats/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradual onset of ictus</td>
<td>Epileptic seizures begin suddenly, but are often preceded by auras</td>
</tr>
<tr>
<td>Prolonged duration</td>
<td>Epileptic seizures usually last &lt; 4 min, but any seizure type can be prolonged; distinguish between ictal and postictal states</td>
</tr>
<tr>
<td>Thrashing, struggling, crying, pelvic thrusting, side-to-side rolling, wild movements</td>
<td>Bizarre complex automatisms can occur with frontal lobe CPS</td>
</tr>
<tr>
<td>Intermittent arrhythmic, out-of-phase jerking</td>
<td>GTCS jerking is rhythmic and usually in-phase</td>
</tr>
<tr>
<td>Clonic activity that abruptly ends</td>
<td>At the end of GTCS, the interval between jerks becomes progressively longer</td>
</tr>
<tr>
<td>Motor activity stops and starts</td>
<td>Extremely rare in isolated seizures; distinguish from a series of seizures</td>
</tr>
<tr>
<td>Ability to talk while “unresponsive”</td>
<td>Automatic speech can occur with right temporal CPS</td>
</tr>
<tr>
<td>Preserved consciousness with bilateral tonic or clonic movements and speech</td>
<td>Supplementary motor area seizures may have bilateral convulsive movements</td>
</tr>
<tr>
<td>Convulsive movements of extremities without facial involvement</td>
<td>Facial involvement in GTCS can be subtle</td>
</tr>
<tr>
<td>Gradual offset of seizure postictal state</td>
<td>Epileptic seizure activity usually ends abruptly, but can merge into</td>
</tr>
<tr>
<td>Features fluctuate from one seizure to the next</td>
<td>Epileptic seizures are usually stereotypic</td>
</tr>
<tr>
<td>Lack of postictal confusion</td>
<td>Often absent after frontal lobe, and less often, temporal lobe, CPS</td>
</tr>
<tr>
<td>Postictal crying or shouting</td>
<td>Aggressive verbal and physical behavior can occur after epileptic seizures if patients are restrained</td>
</tr>
<tr>
<td>Suggestibility (ability to talk someone into or out of the seizure)</td>
<td>Stress of suggestive testing very rarely triggers an epileptic seizure</td>
</tr>
<tr>
<td>No injuries after many recurrent seizures</td>
<td>Injuries may also occur with NES, particularly in patients with a history of self-injury</td>
</tr>
<tr>
<td>Tongue biting at the tip</td>
<td>Tongue biting in epileptic seizures typically is on the side of the tongue</td>
</tr>
</tbody>
</table>

*CPS - complex partial seizure; GTCS - generalized tonic-clonic seizure*
## Psychogenic Non-epileptic Seizures

<table>
<thead>
<tr>
<th>Features suggestive of Non-epileptic seizures</th>
<th>Important Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrashing, struggling, crying, pelvic thrusting, side-to-side rolling, wild movements</td>
<td>Bizarre complex automatisms can occur with frontal lobe seizures</td>
</tr>
<tr>
<td>Preserved consciousness with bilateral tonic or clonic mtos</td>
<td>Frontal lobe seizures may have bilateral convulsive movements without impairment of consciousness</td>
</tr>
<tr>
<td>Lack of postictal confusion</td>
<td>Post-ictal confusion is often absent after frontal lobe seizures</td>
</tr>
<tr>
<td>Postictal crying or shouting</td>
<td>Aggressive and emotional behavior can occur after epileptic seizures</td>
</tr>
</tbody>
</table>
Psychogenic seizures are a common symptom of conversion or somatization disorder and should be recognized as a disabling psychiatric illness requiring treatment.

In many cases, the mechanism underlying psychogenic seizures is never identified, as patients may be resistant to psychologic or psychiatric intervention. Although the diagnosis is difficult for both physician and patient to confront, learning the diagnosis and, usually, following through with treatment controls NES in approximately 50% of patients.

Psychogenic NES must be distinguished from malingering, or consciously feigning epileptic seizures.
Distinguishing epilepsy from mimics of epilepsy often requires video EEG monitoring in an inpatient Epilepsy monitoring unit (EMU). A definitive diagnosis of non-epileptic events is essential to avoid unnecessary treatment with anti-epileptic drugs. EMUs also important to the care of people with known epilepsy. They provide safe environments for withdrawal of antiepileptic seizure medications and observation of seizures for pre-surgical evaluation. They also allow for the recognition of unrecognized seizures which is important part of patient education, particularly if driving is at issue.
Utility of epilepsy video/EEG monitoring units: Non-epileptic spells

Study of 213 EMU admissions
  • 21% had purely nonepileptic events
  • Treated as if epilepsy for a mean of 9 yrs
  • Half treated w/ ≥3 AEDs
  • EMU yielded definitive diagnosis in 88%

Utility of epilepsy video/EEG monitoring units (EMU): Epilepsy

Early Identification of Rcfra tory Epilepsy n=525

- 192 (37%) patients were refractory.
- Only 11% of patients became seizure-free if the first drug was ineffective.
- Suggests need for early pre-surgical evaluation

Patient awareness of seizures n=31

- 30% patients deny all seizures
- Only 23% were aware of all seizures

American Epilepsy Society 2015
Sudden Unexplained Death in Epilepsy: SUDEP

Definition:

“Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (seizure duration >30 min or seizures without recovery in between), in which postmortem examination does not reveal a cause of death”

SUDEP Definitions - Updated

- SUDEP definitions updated in 2012 to recognize that:
  - Some cases of sudden death have insufficient information to determine cause of death
  - Some patients with SUDEP have coexisting conditions that may (in conjunction to seizure) contribute to death (e.g. long QT syndrome)
  - Recognize the concept of near-SUDEP, a patient resuscitated after a probable SUDEP
Epidemiology of SUDEP

SUDEP

- Represents about 2-18% of deaths among the general population of patients with epilepsy. Forsgren et al, Epilepsia 2005; 46 Suppl 11:18
  - Likely most common disease-related cause of death in refractory epilepsy
- Risk of sudden death in epilepsy patients 24X that of general population. Ficker et al, Neurology 1998; 51:1270
SUDEP Incidence

- 100 fold range in SUDEP incidence
- Rates depend on the population studied:
  - Incidence cohort of newly diagnosed epilepsy: 0.09 per 1000 person-years
  - Refractory epilepsy patients: 2.2-6.0 per 1000 p-y
  - Surgical patients: 6.3-9.3 per 1000 p-y
  - Low rates in children but higher rates in adults with childhood onset epilepsy

Sudden Unexplained Death in Epilepsy: SUDEP


- 13/135 SUDEP cases were witnessed.
- 12/15 were associated with a convulsive seizure.
- One collapse occurred 5 minutes after a GTC seizure and one after an aura.
- One patient died in a probable postictal state.
- 12/15 were noted to have experienced respiratory difficulties.
  - Suggests that respiratory dysfunction may be an important contributing factor in SUDEP.
  - Suggests that positioning or stimulation of respiration may be important in the prevention of SUDEP.
# SUDEP Risk Factors

<table>
<thead>
<tr>
<th>Factors associated with increased SUDEP risk</th>
<th>Factors associated with decreased SUDEP risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent GTCs***</td>
<td>Seizure freedom</td>
</tr>
<tr>
<td>Symptomatic ctiology</td>
<td>Sharing bedroom/monitoring</td>
</tr>
<tr>
<td>Nocturnal seizures*</td>
<td></td>
</tr>
<tr>
<td>Subtherapeutic AED levels</td>
<td></td>
</tr>
<tr>
<td>AED polytherapy**</td>
<td></td>
</tr>
<tr>
<td>carbamazepine use</td>
<td></td>
</tr>
<tr>
<td>lamotrigine use</td>
<td></td>
</tr>
<tr>
<td>Early age of epilepsy onset/longer duration of epilepsy**</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
</tr>
<tr>
<td>Mental retardation</td>
<td></td>
</tr>
</tbody>
</table>

* Risk factors found in multiple studies.


American Epilepsy Society 2015
SUDEP: Mechanisms

- Witnessed, EMU-recorded, and post-mortem studies all support a seizure, typically GTC, as the terminal event.

- Three main mechanisms emerge from observed cases:
  - Primary respiratory causes: central or obstructive apnea
  - Cerebral shutdown: diffuse post-ictal suppression of EEG preceding EKG or respiratory changes
  - Cardiac arrhythmias/autonomic failure

Friedman, et al. JCI 2013; 123: 1415. [PMID: 23524959]
SUDEP Prevention

Evidence suggests seizure control reduces SUDEP risk
- Meta-analysis showed adjunctive treatment was effective in reducing risk of SUDEP during the observation period compared to placebo in addition to AEDs.

Optimize seizure control as promptly as possible
- Re-evaluate epilepsy diagnosis and treatment as soon as 2 AEDs have failed or when GTC seizures are frequent despite initial AED treatment.
- Evaluate for other therapies: surgery, VNS, diet therapy.
- Maximize adherence to AEDs.
- Address seizure-provocative lifestyle factors (alcohol use, sleep deprivation).

Educate patients and families

Seizure alert devices
- Several devices (watches, bed motion detectors) exist to alert caregivers for GTC seizures.
- Caution: none are FDA approved or proven to prevent SUDEP or other complications of seizures.
First Aid

Tonic-Clonic Seizure

- After seizure ends, turn person on side with face turned toward ground to keep airway clear, protect from nearby hazards

- Transfer to hospital needed for:
  - Multiple seizures or status epilepticus
  - Person is pregnant, injured, diabetic
  - New onset seizures

- Do NOT put any object in mouth or restrain
Epilepsy is unique in the variety of legal problems that it creates. Among these, none engenders as much debate and controversy as driving. All states regulate driving by persons with epilepsy. The appropriate seizure-free interval before driving is permitted may be prescribed or suggested by each state board, but often the privilege of driving is based on a physician statement concerning the particular patient. Most states rely on applicants to disclose their medical condition relevant to driving. Some states (currently six) mandate physician reporting.

Medical statements are scrutinized by a medical review board which typically includes neurologists. The board either permits driving or specifies the period of restriction before driving may be legally resumed. Prescribed seizure-free periods for driving vary from three months to two years.

Driving by people with epilepsy poses a small but identifiable risk to public safety, whereas individual risks to patients may be greater. It is a difficult task to devise an effective method of monitoring driving safety among people with epilepsy that is not discriminatory and at the same time protects both the patient and his or her surroundings.
Pregnancy and Epilepsy Guidelines for Management

- 50% of pregnancies in women with epilepsy are unplanned
- All women with epilepsy of reproductive age should be counseled about the effects of epilepsy and AEDs on a future pregnancy
- Pregnancy planning starts with the first AED prescription for a woman of childbearing age and drug changes should be made a year before conception when possible

American Epilepsy Society 2015
A major concern of women of childbearing age is the teratogenic potential of AEDs. Whereas the incidence of major birth defects (those requiring medical or surgical intervention) in the normal population is approximately 2-3%, approximately twice as many, or 4-7%, of the offspring of women on AED monotherapy have recognizable major birth defects, with another 5-10% having minor cosmetic anomalies such as shortened distal digits. AEDs are felt to be the major reason for the increased risk of fetal malformations, though some may be related to injury imposed by seizures during the pregnancy or genetic abnormalities carried by the mother. While physicians can do little about the latter, there is an obvious tension between the first two risk factors, optimal control of maternal seizures vs. teratogenicity of AEDs (particularly in early pregnancy).
A wide variety of birth defects are associated with the use of virtually all AEDs. Among the most serious major birth defects are neural tube defects (spina bifida and anencephaly). Since there is evidence that folic acid supplementation can decrease the risk of these defects, many neurologists provide supplemental folate to all women of childbearing age under treatment for epilepsy.
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The available data on major congenital malformations and AEDs come from various population-based, hospital-based and pharmaceutical based pregnancy registries. These registries utilize different methods of data ascertainment making it difficult to compare data across studies and data on several of the newer AEDs is still limited. Valproate, however, has been consistently associated with higher rates of fetal malformations.
## AEDs in Pregnancy

- **Probably safest AEDs** (range of published MCM rates)
  - Lamotrigine (2-3.2%)
  - Levetiracetam (3%)
  - Carbamazepine (2.2-6.3%)
  - Phenytoin (2.9-6.7%)
- **Probably have risk lower than valproate**
  (more data needed)
  - Oxcarbazepine
  - Zonisamide
  - Gabapentin
- **Have significant risk greater than some other AEDs**
  - Topiramate
  - Phenytoin
  - Valproate

Adapted from Harden CL. Continuum. 2014; 20:60–79 [PubMed]
Pregnancy and Epilepsy Guidelines for Management

Education

- Most women with epilepsy have normal children.
- Risk of fetal malformations is increased with AED exposure.
- AED teratogenicity is related to exposure in the first trimester of pregnancy.
- Effects on cognitive development likely occur throughout pregnancy but particularly in 3rd trimester.
- Planning should begin well before pregnancy.
- Seizures may be deleterious to the fetus.
- Compliance with AED treatment is important.
- Prenatal diagnosis of fetal malformations is possible.
Pregnancy and Epilepsy Guidelines for Management

Before pregnancy

- Confirm epilepsy diagnosis (exclude non-epileptic seizures)
- Attempt AED monotherapy with lowest effective dose
- Consider switching AEDs prior to pregnancy, particularly if on valproate
- Establish baseline therapeutic levels
- Folate supplementation
  - 0.4 – 5 mg/day
Pregnancy and Epilepsy Guidelines for Management

During pregnancy
- Continue folate supplementation
- Recommend level II ultrasound
- Monitor AED levels at least monthly and adjust dose accordingly
  - Lamotrigine clearance increases dramatically over the course of pregnancy
  - Metabolism also increased for levetiracetam, oxcarbazepine, phenobarbital and phenytoin
  - Carbamazepine levels may be relatively stable, but depends on the individual patient
  - Patients need a post-partum dosing plan to avoid toxicity post-partum
Breast Feeding and Epilepsy

- Breastfeeding should be encouraged for most women with epilepsy
- Known benefits of breastfeeding likely outweigh theoretical risks of medication exposure for most drugs
- Six year old breastfed children of mothers taking carbamazepine, lamotrigine, phenytoin or valproic acid monotherapy had higher IQs and verbal abilities than children who were not breastfed. No adverse effects were noted
- Some recommendations advise caution with drugs with longer half-lives including ethosuxamide, phenobarbital and zonisamide but concerns are mostly theoretical. More data is needed on these drugs

Appendix:
References for Neurologists

Epidemiology and classification


Appendix:
References for Neurologists

**Evaluation of a first seizure**


Appendix:
References for Neurologists

Anti epileptic drugs


Appendix:
References for Neurologists

Anti-epileptic drugs in special populations


Appendix:
References for Neurologists

Discontinuing antiepileptic drugs

- Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic

- Practice parameter: a guideline for discontinuing antiepileptic drugs in
seizure-free patients—summary statement. Report of the Quality Standards

- Specchio LM et al. Discontinuing antiepileptic drugs in patients who
are seizure free on monotherapy. J Neurol Neurosurg Psychiatry 2002
72: 22-25 [PubMed]
Appendix:
References for Neurologists

Intractable epilepsy and epilepsy surgery

Appendix:
References for Neurologists

Management of status epilepticus


<table>
<thead>
<tr>
<th>Seizure type or epilepsy syndrome</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Level of efficacy and effectiveness evidence (in alphabetic order)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with partial-onset seizures</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>Level A: CBZ, LEV, PHT, ZNG Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB</td>
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<tr>
<td>Children with partial-onset seizures</td>
<td>1</td>
<td>0</td>
<td>19</td>
<td>Level A: OXC Level B: None Level C: CBZ, PB, PB, PHT, TPM, VPA, VGB</td>
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<tr>
<td>Elderly adults with partial-onset seizures</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Level A: GBP, LTG Level B: None Level C: CBZ</td>
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<tr>
<td>Adults with generalized seizures</td>
<td>0</td>
<td>0</td>
<td>27</td>
<td>Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA</td>
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<tr>
<td>Children with generalized seizures</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA</td>
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<tr>
<td>Children with absence seizures</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>Level A: ESM, VPA Level B: None Level C: LTG</td>
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<tr>
<td>SPCTR</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>Level A: None Level B: None Level C: CBZ, VPA</td>
</tr>
<tr>
<td>JME</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>Levels A, B, C, None</td>
</tr>
</tbody>
</table>


American Epilepsy Society 2015
## Recommendation Levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Established as useful/predictive or not useful/predictive for the given condition in the specified population.</td>
</tr>
<tr>
<td>B</td>
<td>Probably useful/predictive or not useful/predictive for the given condition in the specified population.</td>
</tr>
<tr>
<td>C</td>
<td>Possibly useful/predictive or not useful/predictive for the given condition in the specified population.</td>
</tr>
<tr>
<td>U</td>
<td>Data inadequate or conflicting. Given current knowledge, test, predictor is unproven.</td>
</tr>
</tbody>
</table>

Clinical Epilepsy Workgroup

- Daniel Friedman, MD (chair)
- Elizabeth E. Gerard, MD (past chair)
- Ed Garcia, MD
- Sara Inati, MD
- Mina El-Hagassy, MD
- David Ko, MD
- Siddhartha Nadkarni, MD

Prior members:
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- Alan Ptringer, MD