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.
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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**. Secondarily 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; deja 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.
EEG: Typical Absence Seizure
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
Atonic and tonic seizures, like atypical absence, are most common in people with other neurologic abnormalities in addition to epilepsy.

In contrast to partial motor seizures, tonic seizures are generalized, involving bilateral musculature in a symmetric or nearly symmetric manner. Tonic seizures are 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. They typically occur during sleep and 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 electrodcremental 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. The EEG shows generalized polyspikes, 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.

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).

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>
</tr>
<tr>
<td>Hypo- or hyperkalemia</td>
<td>Rare to cause seizure. Sometimes through hypomagnesemia</td>
</tr>
<tr>
<td>Hypo- or hypercalcemia</td>
<td>Usually other seizures first, such as tetany or altered consciousness</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>BS $&lt;$50, disrupted Na/K pump</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>May exacerbate epilepsy but rarely is de novo cause</td>
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</tbody>
</table>

BS = blood sugar.

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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
- Penicillins
- Cyclosporin
- Methadone
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.

The EEG Abnormalities

- Background abnormalities: significant asymmetries and/or degree of slowing inappropriate for clinical state or age
- Interictal abnormalities associated with seizures and epilepsy
  - Spikes
  - Sharp waves
  - Spike-wave complexes
- May be focal, lateralized, generalized
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.
Medical Treatment of First Seizure

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.
Choosing Antiepileptic Drugs

- 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 depends largely on drug side-effect profile and patient’s preference/concerns
- Choice of AED for generalized epilepsy depends on predominant seizure type(s) as well as 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 and rufinamide are newer antiepileptic drugs approved by the FDA since 1993. These drugs mark the beginning of new treatment options for epilepsy, and several new AEDs are likely to be approved within the next few years. After randomized clinical trials, all nine 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. Lacosamide was recently (October 2008) approved by the FDA as adjunctive therapy in partial-onset seizures based on two phase III clinical trials that demonstrated it’s efficacy over placebo as add-on therapy. In practice, much of the choice of antiepileptic 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
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.
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 it’s association with polycystic ovarian syndrome and teratogenicity.
Choosing Antiepileptic Drugs (cont.)

Myoclonic Seizures

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

**Possibly effective:**
- Zonisamide, Topiramate
Choosing Antiepileptic Drugs (cont.)

Lennox-Gastaut Syndrome

Best evidence/FDA indication*:
- Topiramate, Felbamate, Clonazepam, Lamotrigine, Rufinamide, Valproate
* FDA approval is for adjunctive treatment for all except clonazepam

Some evidence of efficacy:
- Zonisamide, Levetiracetam
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.
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.
## AEDs and INR

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

*AEDs increase metabolism of warfarin, but warfarin is 99% protein bound, and PHT and VPA increase warfarin’s free fraction.

Antiepileptic Drug Interactions

Drugs that may decrease the efficacy of oral contraceptive pills:

- Phenytoin
- Carbamazepine
- Phenobarbital
- Topiramate*
- Oxcarbazepine*
- Felbamate*

* at high doses

"High-dose" birth control pills are recommended for patients taking these medications.
Antiepileptic Drug Interactions

- Lamotrigine and hormonal contraception:
  - Oral contraceptive pills can decrease lamotrigine levels by 30%
  - Lamotrigine levels will increase significantly during the placebo week, possibly leading to toxicity
  - Lamotrigine can decrease progesterone levels. Patients using Depo-provera may need shorter intervals between injections.
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.
Adverse Effects of AEDs:
Common

Typically dose-related:
Dizziness, Fatigue, Ataxia, Diplopia
• all AEDs

Irritability
• levetiracetam

Word-finding difficulty
• topiramate

Weight loss/anorexia
• topiramate, zonisamide, felbamate

Weight gain
• valproate (also associated with polycystic ovarian syndrome)
• carbamazepine, gabapentin, pregabalin
Adverse Effects of AEDs: Serious

Typically Idiosyncratic:

Renal stones
  • topiramate, zonisamide

Anhydrosis, heat stroke
  • topiramate

Acute closed-angle glaucoma
  • topiramate

Hyponatremia
  • carbamazepine, oxcarbazepine
Adverse Effects of AEDs: Serious

Typically Idiosyncratic:

Aplastic anemia
- felbamate, zonisamide, valproate, carbamazepine

Hepatic Failure
- valproate, felbamate, lamotrigine, phenobarbital

Peripheral vision loss
- vigabatrin

Rash
- phenytoin, lamotrigine, zonisamide, carbamazepine
Adverse Effects of AEDs: 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

Adverse Effects of AEDs: 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

- ▲▲ = rash rate significantly greater than average of all other AEDs (p<0.003)
- ▼▼ = 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)

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Adverse Effects of AEDs: 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, Phillipines and Taiwan
2-4% in India
<1% in Japan and Korea

58/90 Asian patients w/ SJS/TEN had this allele vs 4% of CBZ 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)

www.fda.gov
Epilepsy Comorbidities and AEDs

Osteoporosis
- Mostly worsened by the enzyme inducers: phenytoin, phenobarbital, primidone. Carbamazepine data equivocal.
- Equivocal data with valproate, unavailable for other non-inducers.
- Patients should take calcium 1000-1500/day, Vit D 400-4000/day

Migraine
- Consider topiramate, valproate

Depression
- Can be exacerbated by levetiracetam (and less so zonisamide)
- Can be helped by lamotrigine and possibly gabapentin, pregabalin (and vagus nerve stimulator)
Depression in Epilepsy

- Prodromal, peri-ictal, interictal
- 20% to 60% in many series
- Suicide rate 5 times higher than that of general population

Depression in Epilepsy

Depressive Symptoms in Epilepsy

- Severe Depression
- Mild/Mod Depression
- No Depression

Epilepsy: 26.4% Severe, 63.5% Mild/Mod, 10.0% No Depression
Asthma: 20.2% Severe, 72.3% Mild/Mod, 7.6% No Depression
No Chronic: 8.2% Severe, 88.1% Mild/Mod, 9.6% No Depression

Score Cutpoints: Major Depression > 21, Mild/Moderate Depression = 15-21, No Depression < 15
CES-D: overall group effect (p < 0.001), comparison between epilepsy and asthma groups (p = 0.05).


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Bipolar Depression in Epilepsy

Bipolar symptoms in epilepsy and other chronic conditions

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
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.
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.
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.

Neuroimaging 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.

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 metaanalysis 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 Metaanalysis 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 Callosotomy
- Palliative surgery for intractable epilepsies with drop attacks
  (i.e. Lennox-Gastaut Syndrome)
- Up to 73% have > 73% 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 connections
- Generally reserved for epileptogenic regions in functional cortex

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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.
Status epilepticus is defined as: 1) an episode of more than 10 minutes of continuous seizure activity, or 2) two or more sequential seizures spanning this period without full recovery between seizures. Clinically, however, 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
SE Treatment Algorithm

One commonly used treatment algorithm is:

First 5 minutes:
- Check emergency ABC’s
- Give O2
- Obtain IV access
- Begin EKG monitoring
- Check fingerstick glucose
- Draw blood for Chcm-7, Magnesium, Calcium, Phosphate, CBC, LFTs, AED levels, ABG, troponin
- Toxicology screen (urine and blood).

SE Treatment Algorithm

6-10 minutes
- Thiamine 100 mg IV; 50 ml of D50 IV unless adequate glucose known.
- Lorazepam 4 mg IV over 2 mins; if still seizing, repeat X 1 in 5 mins.
- If no rapid IV access give diazepam 20 mg PR or midazolam 10 mg intranasally, buccally or IM.

SE Treatment Algorithm

10-20 minutes:
- If seizures persist, begin fosphenytoin 20 mg/kg IV at 150 mg/min, with blood pressure and EKG monitoring.
- Reasonable to bypass this step, or perform subsequent step simultaneous with fosphenytoin loading

SE Treatment Algorithm

10-60 minutes: one (or more) of the following 4 options:
(intubation usually necessary except for valproate)

- Continuous IV midazolam: Load: 0.2 mg/kg; repeat 0.2-0.4 mg/kg boluses every 3 minutes until seizures stop, up to a maximum total loading dose of 2 mg/kg. Initial rate: 0.1 mg/kg/hr. Infusion range: 0.05 – 2.9 mg/kg/hr.

OR

- Continuous IV propofol: Load: 1 mg/kg; repeat 1-2 mg/kg boluses every 3-5 minutes until seizures stop, up to maximum total loading dose of 10 mg/kg. Initial infusion rate: 2 mg/kg/hr. Infusion range: 1-15 mg/kg/hr. Avoid >48 hours at >2 mg/kg/hr (increased risk of propofol infusion syndrome).

OR

- IV valproate: 40 mg/kg over ~10 minutes. If still seizing, additional 20 mg/kg over ~5 minutes.

OR

- IV phenobarbital: 20 mg/kg IV at 50-100 mg/min.


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SE Treatment Algorithm


60 minutes:
- Continuous IV Pentobarbital. Load: 5 mg/kg at up to 50 mg/min; repeat 5 mg/kg boluses until seizures stop. Initial CI IV rate: 1 mg/kg/hr. CI IV-dose range: 0.5-10 mg/kg/hr; traditionally titrated to suppression-burst on EEG.

Begin EEG monitoring ASAP if patient does not rapidly awaken, or if any CIV treatment is used.
- ~20% of those patients successfully treated clinically 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><strong>Pallor</strong></td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Cyanosis</strong></td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Loss of consciousness</strong></td>
<td>&lt;20 secs</td>
<td>&gt;60 secs</td>
</tr>
</tbody>
</table>

Tirach et al., Merritt's Textbook of Neurology, 2007

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## 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>


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# Syncope vs Seizure: During Spell

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


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<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>

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Features That Are Not Helpful in Differentiating Syncope from Seizure

- Incontinence
- Prolactin level
- Dizziness
- Fear
- Injury other than lateral tongue biting
- Eye movements (rolling back)
- Brief automatisms

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 phenomena. Migraine 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.
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
- Opisthotonus
- Side-to-side head shaking
- Prolonged duration (>4 minutes)
- Stopping and starting
- Suggestibility
## 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 mts</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>

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<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Convulsions/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset: sudden</td>
<td>Epileptic seizures begin suddenly, but are often preceded by aura.</td>
</tr>
<tr>
<td>Prolonged duration</td>
<td>Epileptic seizures usually last ≤ 4 min, but any seizure type can be prolonged; distinguish between ictal and postictal states.</td>
</tr>
<tr>
<td>Thrashing, screaming, crying, pelvic thrusting, side-to-side rolling, wild movements</td>
<td>Throats crotches automations can occur with frontal lobe CPS.</td>
</tr>
<tr>
<td>Intermittent rhythmic, 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>Exerted force in ictal seizures; distinguish from a series of sciences.</td>
</tr>
<tr>
<td>Ability to talk while &quot;unresponsive&quot;</td>
<td>Automatic speech can occur with right temporal CPS.</td>
</tr>
<tr>
<td>Tense, rigid posture with brachial and axial movements and speech</td>
<td>Supplementary zones 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 seizures</td>
<td>Epileptic seizure activity usually ends abruptly, but can merge into postictal phase.</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, converse in and out of the seizure)</td>
<td>Stress of suggestive testing can trigger 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>

*CP·S - complex partial seizure, GTCS - generalized tonic-clonic seizure*
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 presurgical 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 Refractory 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

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Sudden Unexplained Death in Epilepsy: SUDEP

Definition:

“sudden, unexpected, witnessed or unwitnessed, nontraumatic and non-drowning death in a patient with epilepsy where the postmortem examination does not reveal a toxicologic or anatomic cause of death, with or without evidence of a seizure and excluding documented status epilepticus.”

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.
Epidemiology of SUDEP

SUDEP

- Represents about 2-18% of deaths among the general population of patients with epilepsy.

- Risk of sudden death in epilepsy patients 24 X that of general population.

- Mean SUDEP incidence: 3.7/1000 people per year.
  - Higher in patients referred for epilepsy surgery (up to 1 per 100 per year).

Epidemiology of SUDEP

SUDEP Risk Factors

- History of and number of GTCS
- Frequent seizures
- Subtherapeutic AED levels
- Young adults
- Long epilepsy duration; early epilepsy onset
- AED polytherapy
- Frequent AED changes
- IQ <70

Recommendations for SUDEP prevention

Optimize seizure control as promptly as possible
- Re-evaluate epilepsy diagnosis and treatment as soon as 2 AEDs have failed, or when GTC szs are frequent despite initial AED treatment
- Consider epilepsy surgery at that point
- Maximize compliance with AEDs

Use the least number of AEDs needed to control seizures
- Add AED with the aim of replacing the current AED in a timely fashion (But not at the expense of worsening of seizure control)

Educate patients and families
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.
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
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.
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 later, there is an obvious tension between the first two risk factors, optimal control of maternal seizures vs. teratogenicity of AEDs (particularly in early pregnancy).
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.
Pregnancy and Epilepsy: Major Congenital Malformation and AEDs

MCM rate similar among other studied AEDs in monotherapy, but not enough data to show significant difference between them:
- Levetiracetam
  - Early data promising (0% in monotherapy, 2.7% in polytx)
- Carbamazepine (2.2-3.9%)
  - Substantial data available, relatively good track record
- Lamotrigine (1.4-4.4%)
  - Increased risk (5.4%) with doses > 400/day
- Gabapentin (0-3.2%)
- Topiramate (0-4.8%)
- Phenytin (3.2-6.7%)
- Zonisamide, Pregabalin
  - Limited monotherapy data

Pregnancy and Epilepsy Guidelines for Management

All women of child-bearing potential should receive education and carefully considered management before and during pregnancy to optimize the chances of a good outcome for both mother and child.

Pregnancy and Epilepsy: Major Congenital Malformation Rates in Monotherapy

![Graph showing congenital malformation rates in pregnant women with epilepsy treated with different antiepileptic drugs.](image)


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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
- 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
- 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

- Monitor AED dose requirements to maximize seizure control

- Particularly with lamotrigine (levels fall > 50% and sz increase)

- Also increased clearance of levetiracetam, oxcarbazepine, phenobarbital and phenytoin

- Continue folate supplementation

- High-risk OB care, consider prenatal diagnosis of malformations, level II ultrasound

- Consider Vit K (10 mg/day orally) starting at 36 weeks
Breast Feeding and Epilepsy

Breastfeeding should be encouraged unless clear risk posed

Probably safe:
- Carbamazepine
- Phenytoin
- Valproate
- Lamotrigine

"Use with caution" in lactating women:
- Pramidone
- Phenobarbital
- Ethosuximide

Pennell et al. Epilepsy and Behavior. 2007. 11: 263-9 [crossref]
Neonatal seizures can be a concerning neurological sign. The significance of neonatal seizures lies in their association with a variety of serious underlying conditions, including hypoxic-ischemic encephalopathy, infection, trauma, stroke, metabolic disease, and malformations of cortical development. Although dependent on the underlying etiology, there is a high rate of mortality and neurologic morbidity. The clinical and electrographic manifestations of neonatal seizures differ from those in older, more neurologically mature individuals. This reflects the functional differences such as a lesser degree of myelination in the developing brain.

The reported incidence of neonatal seizures varies enormously, from 3% to 25%. Some of this variation probably reflects difficulties in diagnosis. Neonatal seizures are associated with increased rates of mortality and chronic neurologic morbidity, with sequelae in as many as 50% to 70%. Neonatal seizures may help identify a treatable disorder that can cause permanent brain injury. For example, hypoglycemia and bacterial meningitis can cause neonatal seizures. In such circumstances, quick and appropriate treatment may halt further progress of the disease and prevent additional damage to the brain.
The diagnosis of neonatal seizures has historically been based on visual inspection, although video-EEG studies have shown that clinical diagnosis of neonatal seizures is unreliable. A neonatal seizure classification system, based on clinical signs, has gradually evolved, and includes clonic, myoclonic, tonic and "subtle" neonatal seizures. There is relatively little problem associated with recognizing focal clonic, focal tonic seizures, and these clinical events have a reliable correlation with ictal activity on EEG. Myoclonic seizures, generalized tonic seizures and subtle seizures are more difficult to diagnose clinically. Although clinical behaviors such as myoclonus, tonic posturing, apnea, tongue thrusting, sucking movements, and ocular nystagmus can be part of clinical seizure, they do not have a high correlation with ictal activity on EEG. Rather these events are termed "automatisms" or "brainstem release signs."
The evaluation of the infant with neonatal seizures should not await EEG confirmation. Management of suspected neonatal seizures pursues a simultaneous triple course: 1) confirm the diagnosis with EEG, 2) evaluate the infant for the cause(s) of the seizures, emphasizing treatable etiologies, and 3) initiate antiepileptic drug (AED) therapy. Many infants with neonatal seizures have underlying medical or neurologic illnesses that cause the seizure, i.e., acute, symptomatic seizures, not an intrinsically "lowered seizure threshold" constituting the substrate of epilepsy.
Phenobarbital remains the most commonly used drug for neonatal seizures. Alternatives include phenytoin and benzodiazepines. Many of the newer AEDs have anecdotal experience in this population and can be used if clinically felt appropriate.

Some neonates subsequently develop chronic seizure disorders, often including refractory conditions such as West or Lennox-Gastaut syndromes. The reported frequency with which chronic epilepsy develops after neonatal seizures varies from 4% to 56% of those surviving the neonatal period.

One of the most difficult tasks in the holistic management of the neonate with seizures is a frank, accurate, realistic discussion of prognosis with the infant’s parents. Neonatal seizures are a sign of danger, and the risks of subsequent death, cerebral palsy, mental retardation, epilepsy, attention/hyperactivity disorders, behavioral disturbances and other related, CNS-based disorders must be carefully assessed and communicated.
Catastrophic Epilepsy Syndromes of Infancy and Early Childhood

These epileptic encephalopathies characteristically are present in early life, and can result from a variety of underlying disturbances. While the age of onset differs among the various syndromes, their common etiologic basis and overlap in clinical and EEG features suggests that they form a spectrum.
1. **West Syndrome** typically begins in the first year, usually between 3 and 8 months, and presents a distinct electroclinical triad of infantile spasms, hypsarrhythmic EEG (chaotic, high voltage activity with multifocal spikes) and psychomotor delay. Flexor spasms are typical, but extensor postures and focal motor features are common. These usually last several seconds each but occur in clusters lasting several minutes or longer. Prenatal and perinatal brain injury, metabolic, degenerative disorders, and neurocutaneous disorders and cerebral malformations are frequently identified. Factors associated with poor prognosis include onset before age 3 months, symptomatic etiology, and multiple seizure types. Neurodevelopment is normal in only 10-15% of affected patients. Pharmacologic agents used to treat West Syndrome include the benzodiazepines, valproate and corticosteroids or corticotrophin (ACTH). More recently, vigabatrin (an inhibitor of the GABA-catabolic enzyme GABA transaminase, not yet currently available in the U.S.) has been introduced with success, especially in patients with tuberous sclerosis. Other therapies reported to be successful include topiramate, zonisamide, and the ketogenic diet. West Syndrome associated with focal cortical dysplasia has been treated by resective surgery.

2. **Lennox-Gastaut Syndrome** is characterized by multiple seizure types, mental retardation and slow spike-wave EEG discharges. Seizures begin at ages 1-7; up to 25% of patients initially present with West Syndrome. Tonic, atonic, atypical absence, and tonic-clonic seizures are common, while myoclonic seizures are less common. The onset of the Lennox-Gastaut syndrome may be gradual or abrupt, but is typically associated with some developmental regression. The prognosis for patients with this syndrome is poor. Multiple seizure types gradually give way to a single predominant pattern by the second decade, while mental impairment and social limitations are permanent. Recurrent bouts of status epilepticus are common, and standard AEDs often produce unsatisfactory seizure control. Onset of the Lennox-Gastaut syndrome before age 2 years has a particularly unfavorable outcome. Corticosteroid therapy may provide short term seizure control and the ketogenic diet has been successful in selected patients. Sodium valproate and lamotrigine are favored by many clinicians, and preliminary studies of topiramate suggest a beneficial role. Felbamate is also beneficial but may have a greater potential for serious adverse events. The ketogenic diet and VNS have also been used with success.

3. **Myoclonic epilepsies** of infancy and early childhood are a heterogeneous group of disorders characterized by differing clinical manifestations of epileptic myoclonus, often associated with generalized or partial seizures, neurodevelopmental delay and generalized EEG abnormalities. The variety of electroclinical presentations has led to a complex and confusing classification system. All patients with myoclonic epilepsy, especially those with developmental delay or regression, should undergo careful evaluation for underlying causes including cerebral dysplasia, tuberous sclerosis,
Febrile Convulsions

Febrile convulsions are the most common seizures in early life, generally occurring between 6 months and 5 years, and have an excellent long-term prognosis. Simple febrile seizures last less than 15 minutes and lack focality. Complex febrile seizures are longer in duration, may have focal manifestations, or recur within 24 hours. The EEG is nonspecific and rarely adds useful prognostic information. MRI is also of little value. In later life, some patients exhibit specific epileptiform patterns indicating a genetic or structural basis for epilepsy.

The diagnosis and management of febrile seizures rests largely with the general practitioner or pediatrician. Prophylactic AEDs should be avoided, although oral diazepam can be given when fevers are identified in susceptible children. Multiple or prolonged attacks can be aborted by administration of rectal diazepam.

Approximately one third of patients with one febrile seizure will have a second or (less commonly) third; recurrences are more common in younger patients. Between 1.5% and 4.6% of children with febrile seizures later develop afebrile seizures, i.e., epilepsy. The higher percentage applies to those with complex febrile seizures (as defined above), and the epilepsy risk may be even greater in those with neurodevelopmental abnormalities.
Idiopathic Partial Epilepsy Syndromes

Two clinical syndromes, benign partial epilepsy with centrotemporal spikes and childhood epilepsy with occipital paroxysms, present distinctive seizure and EEG patterns during the first decade in neurologically normal children. (Slide 60)

1. Benign partial epilepsy with centrotemporal spikes (BECTS) (also known as benign rolandic epilepsy of childhood) is the most common epilepsy syndrome in childhood. Partial seizures typically occur within hours of falling asleep and are characterized by sensorimotor symptoms affecting the face, oropharynx, and occasionally the limbs. Up to 25% of patients develop secondarily generalized seizures. Centrotemporal spikes, more common during sleep, are the electrographic hallmark of the syndrome and indicate focal seizure origin from perirolandic cortex.

At times, children without a seizure history have centrotemporal spikes typical of BECTS on an EEG obtained to evaluate a different complaint; in this situation it should be regarded as an incidental finding. Most symptomatic children with BECTS respond promptly to treatment with first-line AED therapy. A published abstract of a multi-center study by Bourgeois et al suggests that gabapentin may be a good first line AED in this condition. The disorder remits by the middle of the second decade.

2. Benign childhood epilepsy with occipital paroxysms usually begins at ages 4-12 years and accounts for approximately 20% of idiopathic childhood epilepsies. Older patients generally manifest distinct visual phenomena including simple or complex visual hallucinations, visual distortions, hemianopsia and amaurosis. Misdiagnosis as migraine is common (and migraine may co-exist). In younger patients, seizures are less frequent and often nocturnal, but can present more dramatically with prolonged unresponsiveness and convulsions. Both variants may have repetitive occipital discharges on the EEG during eyelid closure. More recently, Panayiotopoulos et al have lumped variations of and inclusive of this epilepsy syndrome under, “Panayiotopoulos syndrome”, with emphasis on prominent autonomic symptoms as well as spike and slow wave patterns that may be more diffuse than simply the occipital regions.

Long-term prognosis for both the early-onset and later-onset variants is good, with remission being the rule by the end of the second decade. However, patients with the later-onset variety may continue to experience partial seizures in adulthood. There is a recognized association of idiopathic occipital epilepsy, celiac disease and occipital calcifications in some patients. Response to first-line AEDs is usually good.
Idiopathic Generalized Epilepsy Syndromes

1. Childhood absence epilepsy typically begins at ages 4-8 years with frequent absence seizures, which may not initially be recognized; tonic-clonic seizures occur in approximately 40%, often beginning near puberty. Development is typically normal, and EEG is characterized by 3 Hz spike-wave complexes activated by hyperventilation. Both absence and tonic-clonic seizures usually respond well to treatment. The traditional AED treatments used have been ethosuximide and valproate. Newer AEDs tried with success include, lamotrigine, levetiracetam and topiramate. Absence seizures usually remit by adolescence, but infrequent tonic-clonic seizures may occur in adulthood, particularly if patients have the less common form known as, juvenile absence epilepsy which typically affects older children and tends to be more refractory.

2. Juvenile myoclonic epilepsy is characterized by onset of generalized tonic-clonic seizures, especially after awakening, beginning typically in adolescence. While some patients have myoclonus resulting in dropping things, this may go unnoticed in many. Diagnosis may not be made until, often under the stress of sleep deprivation or alcohol withdrawal, a tonic-clonic seizure occurs. EEG typically shows generalized spike-wave and/or polyspike-wave complexes, usually faster than 4 Hz. A minority of patients also have absence seizures, and some have photosensitive seizures, which may be diagnosed on strobe light stimulation during routine EEGs. Because both myoclonic and tonic-clonic, as well as absence seizures respond to valproate, this is generally considered the drug of choice in juvenile myoclonic epilepsy. Preliminary studies with lamotrigine, levetiracetam and topiramate show promise as alternative AEDs. These should be considered as alternatives to valproate particularly in women of childbearing age. Although seizure control is usually excellent, drug therapy must typically be continued, since less than 20% of patients seem to outgrow their condition.
Because specific efficacy data in childhood are limited, AED selection for childhood seizures often relies on extrapolation of efficacy studies in adults. Fortunately, the efficacy of most agents in children appears to parallel the adult experience. However, adverse effects and toxicity are often the major determinant of drug selection in any age group. It is not unusual, for example, for parents to request drug withdrawal due to adverse events, even at the cost of seizure exacerbation.

In the infant and young child, interactions of AEDs with milk and infant formulas are a potential problem. Administration of AEDs while feeding should be avoided in this population. Maturational factors and variability in absorption and metabolism may indicate attention to serum drug concentration monitoring. Specific problems with adverse effects may also require metabolic monitoring. Most children cannot be expected to reliably swallow tablet or capsule formulations of medication until 8-10 years of age. This makes liquid preparations, chewable tablets and sprinkle capsule formulations attractive alternatives in the younger child and infant. Finally, one must keep in mind that children have constantly changing body mass and metabolism that affect the absorption, distribution and elimination of medication. Regular dosing adjustments with time are needed and younger children typically require a relatively larger dosage of medication in milligrams per kilogram per day than older children and adults.

### AEDs in Pediatrics

- Extrapolation of efficacy data from adult studies
- Importance of adverse effects relative to efficacy
- Susceptibility to specific adverse effects (valproate hepatotoxicity, lamotrigine rash)
- Age-related pharmacokinetic factors
- Neonate: low protein binding, low metabolic rate, possible decreased absorption if given with milk/formula
- Children: faster metabolism
Psychosocial Management
Social and neurobehavioral deterioration are strongly associated with epilepsy onset in childhood. The long-term prognosis of refractory epilepsy is poor and often precludes normal adult functioning. If schooling is compromised, fewer than 5% of patients followed into adulthood function normally. For this reason, it is essential that allied health care practitioners such as neuropsychologists, special educators, and social workers help manage the child with epilepsy.

Ketogenic Diet
Children with seizures that prove intractable to medication or who experience intolerable adverse effects may be candidates for nonpharmacologic therapy with the ketogenic diet. The diet may also allow for simplification of a drug treatment regimen and at times, discontinuation of all AEDs.

Epilepsy Surgery
Children suffering from refractory epilepsy are being increasingly referred for surgery. This trend has resulted from advances in appreciating the poor long-term outlook of these children, identifying neuropathologic substrates of the condition, selecting appropriate patients, and localizing the epileptic focus. A small minority of children with refractory seizures have spontaneous remission, but seizure freedom may not occur for many years, and predicting when remission will occur is virtually impossible. Although there is no long-term comparative data, one would expect that earlier seizure alleviation would contribute to a greater reduction in psychosocial morbidity, a better chance for meaningful education and improved quality of life. Children with intractable epilepsy who are not epilepsy surgery candidates, may benefit from vagus nerve stimulation.
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


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>
</table>
| Adults with partial-onset seizures | 2       | 1        | 30        | Level A: CBZ, PHT  
Level B: VPA  
Level C: GBP, LTG, OXC, PB, TPM, VPA |
| Children with cortical-onset seizures | 1       | 0        | 17        | Level A: OXC  
Level B: None  
Level C: CBZ, PB, PHT, TPM, VPA |
| Elderly adults with partial-onset seizures | 1       | 1        | 2         | Level A: GBP, LTG  
Level B: None  
Level C: CBZ |
| Adults with generalized onset tonic-clonic seizures | 0       | 0        | 23        | Level A: None  
Level B: None  
Level C: CBZ, PB, PHT, TPM, VPA |
| Children with generalized onset tonic-clonic seizures | 0       | 0        | 14        | Level A: None  
Level B: None  
Level C: CBZ, PB, PHT, TPM, VPA |
| Children with obsessive compulsive seizures | 0       | 0        | 4         | Level A: None  
Level B: None  
Level C: CBZ, LTG, VPA |
| DEDS | 0       | 0        | 2         | Level A: None  
Level B: None  
Level C: CBZ, VPA |
| JME | 0       | 0        | 0         | Levels A, B, C: None |


American Epilepsy Society 2010
# AAN’s Recommendation Levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<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>
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<tr>
<td>U =</td>
<td>Data inadequate or conflicting. Given current knowledge, test, predictor is unproven.</td>
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Summary of AAN evidence-based guidelines level A or B recommendations

<table>
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<tr>
<th>AED</th>
<th>Newly Diagnosed Monotherapy Partial/mixed</th>
<th>Newly Diagnosed Absence</th>
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<td>Lamotrigine</td>
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<tr>
<td>Tiagabine</td>
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*Not FDA approved for this indication


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These slides really on a more complicated level than rest of talk

### Summary of AAN evidence-based guidelines level A or B recommendations

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<th>Newly Diagnosed Monotherapy Partial/mixed</th>
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*Not FDA approved for this indication

**Summary of AAN evidence-based guidelines level A or B recommendation**

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<th>Partial Monotherapy</th>
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<td>Yes*(unify absence)*</td>
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* Not FDA approved for this indication


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Confirm Keppra indications?
### Summary of AAN evidence-based guidelines level A or B recommendation

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<th>AED</th>
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* Not FDA approved for this indication

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## Summary of ILAE guidelines on therapeutic drug levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral bioavailability (%)</th>
<th>Serum binding (%)</th>
<th>Time to peak concentration (h)</th>
<th>Time to steady-state (days)</th>
<th>Half-life in the absence of enzyme induction (days)</th>
<th>Half-life in patients undergoing enzyme induction (days)</th>
<th>Common adverse effects</th>
<th>Reference range (mg/L)</th>
<th>Common adverse effects (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>≥85</td>
<td>85</td>
<td>2-4</td>
<td>8-20</td>
<td>10-20</td>
<td>5-10</td>
<td>10-20</td>
<td>0.5-6.5</td>
<td>3.5-15</td>
</tr>
<tr>
<td>Clobazam</td>
<td>&lt;55</td>
<td>85</td>
<td>1-3</td>
<td>7-9</td>
<td>10-20</td>
<td>?</td>
<td>10-20</td>
<td>0.05-0.2</td>
<td>0.2-2</td>
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<tr>
<td>Clozapine</td>
<td>≥55</td>
<td>85</td>
<td>1-4</td>
<td>3-10</td>
<td>0.3-6</td>
<td>0.3-6</td>
<td>0.3-6</td>
<td>0.025-0.65</td>
<td>0.05-3</td>
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<tr>
<td>Clonazepam</td>
<td>≥90</td>
<td>85</td>
<td>1-6</td>
<td>4-6</td>
<td>15-30</td>
<td>10-20</td>
<td>15-30</td>
<td>0.5-10</td>
<td>0.5-10</td>
</tr>
<tr>
<td>Delamanid</td>
<td>≥95</td>
<td>85</td>
<td>1-3</td>
<td>5-6</td>
<td>1.3-1.8</td>
<td>1.2-4.5</td>
<td>1.2-4.5</td>
<td>0.5-2</td>
<td>0.5-2</td>
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<tr>
<td>Lamotrigine</td>
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<td>85</td>
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<td>5-6</td>
<td>1.3-1.8</td>
<td>1.2-4.5</td>
<td>1.2-4.5</td>
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<td>0.5-2</td>
</tr>
<tr>
<td>Levetiracetam</td>
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<td>4-6</td>
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<td>15-30</td>
<td>0.5-10</td>
<td>0.5-10</td>
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<tr>
<td>Oxcarbazepine</td>
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<td>15-30</td>
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<td>0.5-10</td>
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<tr>
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<td>10-20</td>
<td>15-30</td>
<td>0.5-10</td>
<td>0.5-10</td>
</tr>
<tr>
<td>Phenytoin</td>
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<td>Topiramate</td>
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<td>10-20</td>
<td>15-30</td>
<td>0.5-10</td>
<td>0.5-10</td>
</tr>
</tbody>
</table>

*Half-lives are considerably longer after a single dose and are not further increased with increasing serum concentrations. The most common adverse effects are listed in the table (American Epilepsy Society 2010)."