OVERVIEW OF EPILEPSY

Robert Fisher, M.D., Ph.D.,
Maslah Saul MD Professor,
Stanford Neurology
Comprehensive Epilepsy Center, Room A343
300 Pasteur Drive, Stanford, CA 94305-5235

copyright 1997, 2006, 2010

DEFINITION OF EPILEPSY ...................... 2
WHO GETS EPILEPSY? .......................... 3
World Leaders: .................................. 3
Writers and Artists: ............................... 4
Actors: ............................................ 4
Athletes: ......................................... 5
Other public figures: ......................... 5
SEIZURE CLASSIFICATION .................... 5
Partial Seizures .................................. 6
Complex Partial Seizures ...................... 6
Generalized Seizures ............................ 6
Absence Seizures ................................ 6
Tonic-Clonic Seizures ........................... 6
Secondarily Generalized Seizures ............ 7
Atonic Seizures .................................. 7
Myoclonic Seizures .............................. 7
Tonic Seizures ................................... 7
Mixed Seizure Types ............................. 7
What Types are Common? ...................... 7
Classification of Epilepsy Syndromes ...... 7
Localization-Related Epilepsy................ 7
Infantile spasms / West’s syndrome ....... 7
Lennox-Gastaut Syndrome ................. 8
Febrile seizures ................................. 8
Benign Rolandic Epilepsy .................... 8
Juvenile Myoclonic Epilepsy ............... 8
CAUSES (ETIOLOGIES) OF SEIZURES: ...... 8
Causes for Focal Seizures .................... 9
Head Trauma .................................... 9
Stroke ........................................... 9
Infection ....................................... 9
Vascular Malformations ..................... 9
Tumors (Neoplasms) ......................... 9
Dysplasia ...................................... 10
Mesial Temporal Sclerosis ................... 10
Causes for Generalized Seizures .......... 10
Metabolic ...................................... 10
Medication Reactions ........................ 10
Idiopathic (cause unknown) ............... 10
Genetic Causes of Seizures ............... 10
Photosensitive Seizures .................... 11
Medical Imitators of Seizures ................ 12
Psychological Imitators of Epilepsy ...... 13
Circumstances that Provoke Seizures .... 15
Tests for Epilepsy ............................. 16
Postictal: The Aftermath of a Seizure .... 17
MEDICATIONS FOR EPILEPSY ............... 18
General Points ................................. 19
Brief Summary of Antiepileptic Drugs .... 20
Antiepileptic Drug Selection ............... 22
Benzodiazepines: .............................. 23
Carbamazepine (Tegetrol, Novartis; Carbretal) 24
Ethosuximide .................................. 25
Felbamate (Felbatol) .......................... 25
Gabapentin (Neurontin) ..................... 26
Lacosamide (Vimpat) ......................... 27
Lamotrigine (Lamictal) ...................... 28
Levetiracetam (Keppra) ...................... 29
Methsuximide (Celontin) .................... 33
Rufinamide (Banzel) ......................... 34
Tiagabine (Gabitril) ......................... 35
Topiramate (Topamax) ....................... 35
Valproic Acid (Depakote, Depakene, Depacon) 36
Vigabatrin (Sabril) ......................... 37
Zonisamide (Zonegran) ...................... 38
Other Medications ............................ 39
Explaining Prescriptions .................... 39
Switching medicines .......................... 40
Research Testing of New Drugs ........... 40
Stopping Seizure Medicines ............... 41
Uncontrolled (Refractory) Epilepsy ....... 42
EPILEPSY SURGERY ......................... 44
Candidates for Epilepsy Surgery ........... 44
Pre-surgical evaluation .................... 44
Temporal Lobectomy Surgical Procedure ............. 46
Other Surgical Procedures .................................. 47
Surgery Conclusion ........................................... 47
The Ketogenic Diet ......................................... 47
Biofeedback for Seizures ................................... 48
What Can a Person do to Control Seizures? .......... 48
Vagus Nerve Stimulation ................................... 48
The Patient-Doctor Relationship ......................... 49
SOCIAL ISSUES IN EPILEPSY: ............................. 49
  Employment ............................................. 50
  School ..................................................... 51
  Pregnancy ................................................. 51
Risks of Epilepsy ............................................. 53
  Driving ...................................................... 53
  Water Safety ............................................. 53
  Burn safety .............................................. 53
  Heights ..................................................... 54
  Equipment and Power Tools ............................... 54
  Child Care Safety ......................................... 54
Sudden Unexplained Death in Epilepsy (SUDEP) .... 54
Medication Side Effects ..................................... 54
Seizure medicines and suicide ............................. 54
Carbamazepine in Asians and Rash Risk ............... 55
Folic acid to protect from birth defects .................. 55
Birth control pills ........................................... 55
  Bone health ............................................. 55
Recreation ..................................................... 55
Safety Proof Your Environment ............................ 56
Develop a Seizure Safety Plan ............................... 56
For more Information ........................................ 56

DEFINITION OF EPILEPSY

A seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

Therefore, a seizure is the event and epilepsy is the disorder. By definition, one seizure does not make epilepsy, nor does a small series of seizures that have an immediate precipitating factor, for example, alcohol withdrawal seizures. The seizures must be spontaneous and recurrent to represent epilepsy.

Seizures result from an electrochemical disorder in the brain. Brain cells use chemical reactions to produce electrical discharges. Each brain cell either excites or inhibits other brain cells with its discharges. When the balance of excitation and inhibition in a region of brain is moved too far in the direction of excitation, then a seizure can result.

The type of seizure depends upon several factors. One of the most important factors is where in the brain the abnormal electrical discharge occurs. Figure 1 shows the four lobes of the brain (frontal, temporal, parietal and occipital) and where key regions of the brain are located. Strength and sensation are laid out along the border of the frontal and parietal lobes, with strength more toward the front (frontal) and skin sensation more toward the back (parietal) of the strip.

Moving laterally and down the brain are control areas for trunk, arm, hand, fingers, face, lips, and tongue, with tongue most laterally and inferiorly on the motor strip. The progression of electrical activity during a seizure can march through this area activating each muscle group in sequence over seconds to minutes. A talking center, called Broca’s area, is located in the left frontal lobe in front of the motor strip, and a speech comprehension area called Wernicke’s area in the left temporal-parietal region for most right-handers. Speech centers may be on the right or both sides for left-handers. Visual perception is governed from the posterior poles of the occipital lobes. In general, brain functions are crossed: the left side of the brain receives information from, and gives information to, the right side of the body, and vice versa. The reason for this
crossed wiring is lost in evolution, but it started when we were fish.

The undersurface of the temporal lobe is particularly prone to have seizures. The temporal lobes include the parts of the brain most commonly involved in adult epilepsy. Such temporal structures are given Greek names, such as “amygdala” (almond) and “hippocampus” (sea-horse). The amygdala and hippocampus are targets for surgical removal in surgery for epilepsy (see discussion later). These structures are also involved in expression of emotionality and in ability to form memories.

In simple terms, if an abnormal electrical discharge originates in motor cortex: the patient will experience a motor seizure; if in sensory cortex: a sensory perception; if in visual cortex: lights, flashes, or jagged lines. Seizures in deep temporal lobe structures present with arrest of activities, loss of memory or awareness, and automatic (robot-like) behavior. If a seizure spreads to all regions of brain, then a tonic-clonic (grand mal) seizure results, with loss of consciousness, stiffening and jerking.

Before discussing the details of seizures and epilepsy, it is worth making the point that epilepsy is common. Because of the social stigma of this disease, many people with epilepsy do not make it publically known.

WHO GETS EPILEPSY?

Epilepsy is a very common condition. The risk for epilepsy among the U.S. population in general is one percent. Up to 5% or more of the population may have at least one seizure from any cause in their lifetime. Anyone can get epilepsy, from young babies to old men and women. We are learning that epilepsy may have its onset in old age as well as in childhood.

All of the individuals in the figure below had seizures, but not all had epilepsy, defined as spontaneously recurrent seizures.

Since epilepsy affects approximately 1% of the world’s population, it is not surprising to learn that several public and historical figures have had seizures. Particularly for those who lived long ago, the historical record can be uncertain, leading to speculation rather than fact. For others, a diagnosis of seizures is more secure. Some of the public figures probably had acute symptomatic seizures, for example from alcohol withdrawal or a severe medical illness. This would not lead in modern times to a diagnosis of epilepsy, which requires spontaneously recurrent seizures. A few others may have had psychologically generated episodes that imitated seizures. For a scholarly historical review of the subject, see an article by Prof. John Hughes in the journal Epilepsy & Behavior 2005, volume 6, page 115. Let’s consider a few examples of famous people with seizures, divided into categories.

World Leaders:

- Julius Caesar is portrayed as having epilepsy. In the epic movie, Caesar and Cleopatra, starring Richard Burton and Elizabeth Taylor, Caesar expresses his fear of having an attack while he is addressing the Roman populace. The online encyclopedia, Wikipedia, says that Caesar had four documented episodes that might have represented complex partial seizures, and may have had seizures in his youth. However, other conditions have been argued, such as low blood sugar or shaking chills from malaria.

- Alexander the Great, who lived from 356 to 323 BC and conquered much of the known world, may have had epilepsy, but evidence is unsubstantial. He was reported to collapse once after taking a strong medicine for a respiratory ailment brought about by swimming in an icy river, but there is no definite historical record for epilepsy.

- Czar Peter the Great, father of modern Russia, developed a brain infection (encephalitis) at age 21 and thereafter developed seizures with twitching of his left face and left body, and sometimes loss of consciousness.

- Charles V, King of Austria and Holy Roman Emperor in the mid-1500’s suffered from epilepsy, but reportedly even more so from gout. Another Charles, Charles II of Spain was said to be "short, lame and epileptic." Yet another Charles, King Charles II of England developed convulsive status epilepticus in 1685. The treatments he underwent included: “let-
ting" of one pint of blood; an enema of antimony, sacred bitters, rock salt, marrow leaves, violets, beetroot, chamomile flowers, fennel seeds, linseed, cinnamon, cardamon seeds, and aloe; and having his head shaved and blistered. This concoction was not successful.

- Prince John was the youngest son of King George V of England around the time of World War I. Because of the prince’s epilepsy, he was hidden away from the public, until dying from an epileptic seizure at age 13.

- Napoleon Bonaparte is said by Prof. Hughes (Epilepsy & Behavior 2003, volume 4, page 793) to have had symptomatic seizures resulting from kidney failure as well as psychogenic seizures resulting from stress.

- Pope Pius IX, who in the 1800’s became the longest serving pontiff in history, is said by Wikipedia to have had childhood epilepsy and to have died from a heart attack resulting from a seizure.

- Martha Parke Custis, the step-daughter of George Washington, had uncontrolled seizures, and our first president attempted to help her control them with the valerian root, mercury, spring water and bloodletting.

- US President James Madison was said to have either epilepsy or psychogenic seizures, with historian R.A. Rutland (1987) reporting Madison to have monthly “high fevers, diarrhea, and seizures similar to those suffered by epileptics.”

- Vladimir Lenin, revolutionary founder of the Soviet Union, developed seizures in his later years and died from status epilepticus recorded as lasting 50 minutes. In 1919, an assassination attempt left a bullet in his right neck. Three years later it was removed, and shortly thereafter he had three strokes which may have been the cause of his epilepsy. However, other historians argue that he had seizures for years, which were publically ignored because of his political position.

- Senator Ted Kennedy first manifested his brain tumor by having a seizure. Subsequently, he had others.

- US Supreme Court Chief Justice John Roberts had generalized seizures in 1993 and 2007, with no cause released to the public.

**Writers and Artists:**

Many writers, composers and artists have been thought to have had epilepsy.

- Dostoevsky wrote letters speaking of his own epilepsy, which was present by time of his release from a Siberian prison, if not before. Dostoevsky instilled characters with epilepsy into at least four of his novels, and gave detailed descriptions of fictional seizures.

- Another Russian writer, Leo Tolstoy, had convulsions in his last months of life in 1910, as part of a terminal illness.

- Painter Vincent van Gogh is on poster charts for epilepsy organizations as an example of a historical figure with seizures. It is indeed likely that he had seizures, possibly resulting from consumption of potent forms of absinthe liquor (in those years containing toxins) in Paris at the end of the 19th century. He additionally had bouts of manic-depressive illness that could have been mistaken for seizures.

- The author of the novel Mme. Bovary, Gustave Flaubert, had either epileptic or psychogenic seizures.

- The poet, Lord Byron, had several episodes of shaking, foaming at the mouth and unresponsiveness, believed to be either epileptic or psychogenic seizures.

**Actors:**

Several modern actors have been observed to have seizures.

- Richard Burton could consume multiple bottles of vodka in a day, and his seizures may have been from alcohol withdrawal. It was ironically with some personal experience that he acted having a seizure in the film *Caesar and Cleopatra*.

- Bud Abbott, the skinny straight man in the Abbott and Costello comedy team, had epileptic seizures throughout his life, and is said to have attempted to camouflage them with bouts of heavy alcohol consumption.

- Danny Glover, star of many movies including the Lethal Weapon series, has been public about his previous history of epilepsy. Mr. Glover says that he developed "a way of concentrating so that seizures wouldn't happen," and he has been seizure free since age 35.
• Hugo Weaving, who played the leader of the Elves in Lord of the Rings, and the nearly invincible virtual villain in The Matrix, indicates that he has been treated for epilepsy since age 13.

• Margot Hemingway, actress, was the granddaughter of Ernest Hemingway and sister to Mariel Hemingway. Margot Hemingway was taking phenobarbital for lifelong epilepsy, and in possibly died from the combination of phenobarbital and alcohol.

Athletes:

• Florence Griffith Joyner (FloJo) was a world record setting sprinter. Possibly because of abnormal brain blood vessels called cavernous angiomas, she developed seizures and passed away during her sleep from a seizure.

• At least three NFL football stars have publically discussed their seizures. Baltimore Ravens cornerback Samari Rolle indicated that he missed parts of the NFL season because of epilepsy. Jason Snelling was diagnosed with epilepsy at age 15, but still made it to the starting lineup for the Atlanta Falcons. Alan Faneca, the Pittsburgh Steelers Pro Bowl guard, has had epilepsy since his teens. He does extensive volunteer work for the Epilepsy Community.

• Chanda Gunn was goalie in the 2006 Winter Olympics US women's hockey team. She has had seizures since age 9, and serves as a spokesperson for epilepsy and the Epilepsy Therapy Project.

• Bobby Jones, was an NBA basketball player for 13 years, with four years in the All-Stars. He took medications for epilepsy during his athletic career.

Other public figures:

• Alfred Nobel, the inventor of dynamite, and founder of the Nobel Prize once wrote of probable childhood febrile seizures: "I scarce could muster strength to drain the breast, and the convulsions that followed, till I gasped upon the brink of nothingness." It is, however, difficult to find evidence for seizures later in his life.

• Peter Tchaikovsky died from cholera with convulsions at the end of the terminal illness. It has been speculated that blank periods of distraction with automatic behavior earlier in life represented partial seizures, but this cannot be proven.

• Truman Capote, writer of Breakfast at Tiffany's and In Cold Blood had seizures. He was a heavy drinker and the cause may have been alcohol withdrawal.

• Tony Coelho is the former Democratic minority whip of the US House of Representatives. His lifelong experience with epilepsy motivated him to author the landmark legislation Americans with Disabilities Act of 1990. He also served as campaign manager for Al Gore's presidential run. Mr. Coello is the honorary life chair of the Epilepsy Foundation.

• Singer Neil Young, of Crosby, Stills, Nash & Young, thrived despite numerous medical problems, including seizures. He once had a seizure during a concert performance, but he persevered, later remarked commenting, "The aneurysm, polio, epilepsy - all those things are just part of the landscape."

• Entertainer Prince, told interviewer Tavis Smiley in 2009 that he was "born epileptic" and "used to have seizures" but was cured by an angel.

• DJ Hapa is a famous scratch disk jockey with epilepsy. He serves as a spokesperson for the Epilepsy Therapy Project.

• Jet Travolta, son of John Travolta and Kelly Preston, tragically died from a seizure in 2009. Equally tragic was the death of the 6 year-old son of David Cameron, the Prime Minister of the UK.

It is safe to say that many more famous people have epilepsy, but do not reveal it in public because of the ongoing stigma associated with the condition. What lessons can be learned from a list such as the above? Epilepsy can strike anybody at any station of life or level of accomplishment. Epilepsy can be deadly and devastating to a person's life, even if they enjoy other successes. Lastly, epilepsy does not exclude the possibility of major accomplishments and contributions.

SEIZURE CLASSIFICATION

In order to communicate about types of seizures, epilepsy specialists have developed a classification system for seizures. This system is not based on any fundamental property of seizures, but rather on committee-generated conventions of terminology. As such, the classification will change with changes in knowledge about epilepsy. Since the seizure classification describes behaviors during seizures, it is easiest to learn the different types of seizures by watching videotapes of seizures. This is not possible in
a written text, and we will therefore give brief descriptions of the main seizure types.

Table 1 shows the international classification of seizures. Seizures are divided first into two categories: partial (focal) and generalized. Partial seizures have onset on one side of the brain, resulting in focal symptomatology such as twitching in an arm or face, a sensory change, or even the focal type of change in memory that occurs with temporal lobe seizures. Generalized seizures apparently start on both sides of the brain. In fact, epilepsy specialists believe that generalized seizures originate in deep structures of the brain and travel to the cortical surface where we can see the manifestations of the seizure emerge relatively simultaneously.

### Partial Seizures

Partial seizures are further divided into simple partial seizures with no alteration of consciousness or memory, or complex partial seizures with alteration of consciousness or memory. Simple partial seizures can be motor seizures with twitching, abnormal sensations, abnormal visions, sounds or smells, and distortions of perception. Seizure activity can spread to the autonomic nervous system, resulting in flushing, tingling, or nausea. All such simple partial seizures will be in clear consciousness and with full recall on the part of the patient. If the patient becomes confused or cannot remember what is happening during the seizure, then the seizure is classified as a complex partial seizure.

### Complex Partial Seizures

Complex partial seizures previously were called “psychomotor seizures”, “temporal lobe seizures” or “limbic seizures”. These words are all synonyms. Complex partial seizures may have an aura, which is a warning for the seizure, typically a familiar feeling (deja vu), nausea, heat or tingling, or distortion of sensory perceptions. About half of the patients do not have any remembered aura. During the complex partial seizure patients may fumble or perform automatic fragments of activity such as lip smacking, picking at their clothes, walking around aimlessly, or saying nonsense phrases over and over again. These purposeless activities are called automatisms. About 75% of people with complex partial seizures have automatisms. Those who do not simply stop, stare and blank out for a few seconds to minutes.

### Generalized Seizures

Generalized seizures are divided into several categories as listed in Table 1.

### Absence Seizures

Absence seizures previously were called petit mal seizures. Absence seizures usually have onset in childhood, but they can persist into adulthood. Absence seizures present with staring spells lasting several seconds, sometimes in conjunction with eyelid fluttering or head nodding. These seizures can be difficult to distinguish from complex partial seizures that also may result in staring. Absence seizures usually are briefer and permit quicker recovery. The EEG also helps to distinguish an absence from a complex partial seizure (see below).

<table>
<thead>
<tr>
<th>TABLE 1:</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIMPLIFIED INTERNATIONAL CLASSIFICATION OF SEIZURES</td>
</tr>
<tr>
<td>Partial Seizures (Focal, start in one place)</td>
</tr>
<tr>
<td>Simple (no loss of consciousness/memory)</td>
</tr>
<tr>
<td>Sensory</td>
</tr>
<tr>
<td>Motor</td>
</tr>
<tr>
<td>Sensory-Motor</td>
</tr>
<tr>
<td>Psychic (abnl thoughts / perceptions)</td>
</tr>
<tr>
<td>Autonomic (Heat, flushing, GI)</td>
</tr>
<tr>
<td>Complex (loss of consciousness / memory)</td>
</tr>
<tr>
<td>With or without aura (warning)</td>
</tr>
<tr>
<td>With or without automatisms</td>
</tr>
<tr>
<td>Secondarily generalized (spreads)</td>
</tr>
<tr>
<td>Generalized</td>
</tr>
<tr>
<td>Absence, typical or atypical (petit mal)</td>
</tr>
<tr>
<td>Tonic-Clonic (grand mal)</td>
</tr>
<tr>
<td>Myoclonic</td>
</tr>
<tr>
<td>Atonic</td>
</tr>
<tr>
<td>Tonic</td>
</tr>
<tr>
<td>Unclassifiable</td>
</tr>
</tbody>
</table>

### Tonic-Clonic Seizures

Generalized tonic-clonic seizures previously were called grand mal seizures. These seizures start with sudden loss of consciousness and tonic activity (stiffening) followed by clonic activity (rhythmic jerking) of the limbs. The patient’s eyes will roll up at the beginning of the seizure and the patient will typically emit a cry, not because of pain, but because of contraction of the respiratory muscles against a closed throat. Generalized tonic-clonic seizures usually last one to three minutes. The seizure itself is called an ictus. After the seizure, the patient is “post-ictal”:
sluggish, sleepy and confused, variably for hours. Any seizure can have a postictal period. More on this later.

**Secondarily Generalized Seizures**

Seizures that begin focally can spread to the entire brain, in which case a tonic-clonic seizure ensues. It is important, however, to distinguish those that are true grand mal, generalized from the start, from those that start focally and secondarily generalize. Secondarily generalized seizures arise from a part of the brain that is focally abnormal. Drugs used to treat primarily and secondarily generalized tonic-clonic seizures may be candidates for curative epilepsy surgery (see below); whereas, primarily generalized tonic-clonic seizures are not surgical candidates, because there is no seizure origin site (focus) to remove. Seizure surgery is discussed below.

**Atonic Seizures**

Atonic seizures are epileptic drop attacks. Atonic seizures typically occur in children or adults with widespread brain injuries. People with atonic seizures suddenly become limp and may fall to the ground. Football helmets are sometimes required to protect against serious injuries.

**Myoclonic Seizures**

Myoclonic seizure is a brief un-sustained jerk or series of jerks, less organized than the rhythmic jerks seen during a generalized tonic-clonic seizure. Other specialized seizure types occasionally are encountered.

**Tonic Seizures**

Tonic seizures involve stiffening of muscles as the primary seizure manifestation. Arms or legs may extend forward or up into the air. Consciousness may or may not be lost. By definition, the clonic (jerking) phase is absent. Classification can be difficult, because stiffening is a feature of many complex partial seizures. Tonic seizures, however, are much less common than are complex partial or tonic-clonic seizures.

**Mixed Seizure Types**

Patients can have more than one seizure type. One seizure type may progress into another as the electrical activity spreads throughout the brain. A typical progression is from a simple partial seizure, to a complex partial seizure (when the patient becomes confused), to a secondarily generalized tonic-clonic seizure (when the electrical activity has spread throughout the entire brain). The brain has control mechanisms to keep seizures localized. Antiepileptic medications enhance the ability of the brain to limit spread of a seizure.

**What Types are Common?**

Complex partial seizures account for about 40% of all seizure types in adults. Simple partial seizures account for about 20%, primary generalized tonic-clonic seizures about 20%, absence about 10% and other seizure types for 10%. In a pediatric population, absence seizures occupy a greater proportion.

**Classification of Epilepsy Syndromes**

A seizure classification does not specify much about the clinical condition of the patients, for example, cause, severity, or prognosis. An additional classification system therefore has been developed to classify epileptic syndromes. This is a broader classification, since it includes, not just a description of the seizure type, but information about the clinical features of the whole patient.

Syndrome names employ the terms “symptomatic,” “idiopathic,” and “cryptogenic.” Symptomatic implies that the seizures have a known underlying cause, for example, a prior stroke. Idiopathic literally means without known cause. However, among epilepsy specialists, the term has taken on the meaning of epilepsy with genetic causes, and no known structural brain abnormality. Cryptogenic implies that a symptomatic cause is suspected, but not yet found. The whole classification will not be given here, but a few specific epileptic syndromes are worthy of individual discussion.

**Localization-Related Epilepsy**

Localization-related epilepsy connotes partial (focal) seizures. The EEG pattern typically shows a focal electrical abnormality. Prognosis is highly variable, depending upon the cause and location of the focal brain abnormality.

**Infantile spasms / West’s syndrome**

Infantile spasms are a type of symptomatic generalized epilepsy. Spasms appear in children, age 3 months to about 3 years, associated with sudden epileptic flexor spasms and a high risk for cognitive impairment. During flexor spasms, the child may suddenly extend his or her limbs, flex forward at the trunk and emit a cry. The episode is over within seconds, but can recur multiple times per hour. An associated electroencephalographic (EEG, see below) pattern is hypsarhythmia, with high voltage
spikes and a disordered high-voltage background. Early and vigorous treatment of the seizures with the corticoste-
roid stimulating hormone, ACTH, is believed to minimize
the risk for life-long mental retardation and ameliorate the
seizures. Valproic acid and benzodiazepines also are used,
but are not very effective. Among the newer medications,
vigabatrin (Sabril), felbamate, lamotrigine, and topiramate
appear to have a possible role in treatment of infantile
spasms.

Lennox-Gastaut Syndrome

T

he Lennox-Gastaut syndrome, a symptomatic genera-
lized epilepsy, is a relatively rare disorder with the
following criteria: 1. Multiple seizure types, usually includ-
ing atonic or tonic seizures; 2. Variable degrees of cogni-
tive impairment (but not all are impaired); 3. Abnormal
EEG with a slow spike-wave pattern, and other associated
EEG changes. Onset usually is in childhood, but adults
also suffer from this syndrome. Lennox-Gastaut epilepsy
is very difficult to treat, with only 10-20% of patients show-
ing a satisfactory response. Since the epilepsy usually is
widespread in the brain, a focal surgical procedure is not a
good option. The split-brain operation, officially called
corpus callosotomy, can reduce the sudden onset of sei-
zuergs and prevent injuries. Valproate, benzodiazepines,
lamotrigine, vigabatrin, topiramate, zonisamide, levetracet-
tam, rufinamide and felbamate have been tried in this con-
dition, but therapy remains unsatisfactory. A few patients
may respond to vagus nerve stimulators or the ketogenic
diet (see below).

Febrile seizures

A

febrile seizure is a seizure that is provoked by fever.
Febrile seizures tend to present as convulsions (tonic-
clonic) in children age 6 months to 6 years of age. The
clinician must distinguish a febrile seizure from a seizure
with fever caused by some underlying serious condition,
such as meningitis. Although alarming to parents, febrile
seizures usually are benign. Occurrence of a febrile seizure
is a mild risk factor for later development of complex par-
tial epilepsy, but there is no good evidence that trying to
prevent febrile seizures reduces this risk. The large major-
ity of children who have febrile seizures will not go on to
have lifelong epilepsy. This is an important issue, since
seizure medications can impair a child’s learning and per-
sonality. Phenytoin is the usual medication used to
prevent febrile seizures. To work, it must be taken daily,
since by the time of a recognized fever, the seizure usually
already has happened. Daily phenytoin produces hyper-
activity, behavior and learning problems in a significant
fraction of children. Many pediatric neurologists believe
that treatment of febrile seizures is worse than the occa-
sional seizure, and advise no therapy. A few trials of
agents other than phenobarbital have not been encouraging.
Treatment of febrile seizures remains controversial.

Benign Rolandic Epilepsy

B

enign Rolandic epilepsy (BRE) is a seizure type
usually appearing in children or adolescents, around
age 6 to 16 years old. It represents an idiopathic locali-
ization-related epilepsy. The Rolandic region is the area of the
brain at the frontal-parietal, motor-sensory junction. Sei-
zures at this region usually produce twitching or tingling of
a face or hand. Seizures in BRE can secondarily generalize
to tonic-clonic seizures. Seizures are more common upon
falling asleep. EEGs usually show prominent spikes over
the central and temporal areas. The term “benign” is used,
not because individual seizures are minor, but because the
long-term prognosis for outgrowing the seizures by age 21
(usually even earlier) is very good. Depending upon se-
verity of seizures, BRE may or may not be treated with
antiepileptic medications.

Juvenile Myoclonic Epilepsy

J

uvenile myoclonic epilepsy (JME) is the most common
generalized seizure syndrome in young adults. JME
represents a type of idiopathic generalized epilepsy. The
 genetic abnormality has been localized (at least in some
families) to chromosome number 6, and in others to chro-
mosome 20. Patients typically have myoclonus (limb jerk-
ing), and occasional generalized tonic-clonic seizures.
EEG shows a 3-6 per second generalized spike-wave pat-
ttern. Brain MRI is expected to be normal. Responsiveness
to medications, such as valproic acid, lamotrigine, topira-
mate, zonisamide, levetiracetam or benzodiazepines is
good. Unfortunately, the prognosis for outgrowing seizures
in JME is relatively poor, so treatment usually should be
life-long.

CAUSES (ETIOLOGIES) OF SEIZURES:

T

he most common question in an initial epilepsy clinic visit
is “Why do I have seizures”? Since seizures come like
bolts from the blue, it is easy to understand the old supersti-
tions that ascribed seizures to supernatural forces. But sei-
zuergs and epilepsy (the condition of spontaneously recur-
rent seizures) have natural physical causes. What are these causes?

The medical word for “cause” is “etiology.” Etiology of
seizures varies with the type of seizure, whether it starts
locally in one part of the brain or whether it is apparently ge-
neralized all over the brain at the start. Examples of partial-
onset seizures are simple partial (e.g., auras, focal motor),
complex partial (previously called psychomotor or temporal
lobe seizures) and secondarily generalized seizures. Generalized-onset seizures include absence (petit mal), tonic-clonic (grand mal), atonic (drop attacks), myoclonic (sudden jerk) seizures. More information on types of seizures can be found on epilepsy.com at http://www.epilepsy.com/epilepsy/types_seizures and the video series at http://www.epilepsy.com/node/3007.

**Causes for Focal Seizures**

Focal seizures are caused by injury or malfunctioning of one or more parts of the brain. A brain injury may generate an immediate (defined loosely as being within one week of an injury) seizure, but these early seizures often do not lead to later seizures. If recurrent seizures arise more than a week after an injury, then the condition is considered epilepsy. The onset of seizures after a brain injury often occurs after such a delay, even of many years. Researchers believe that this delay results from reorganization of nerve connections in the injured areas. The brain makes an attempt to fix the injury by growing new connections, but the result is a circuit that is more electrically excitable and prone to produce seizures. Here are some of the common brain injuries or conditions that may lead to epilepsy. These etiologies often (but not always!) can be revealed by a brain MRI.

**Head Trauma**

The bumps on the head and the falls from the swings that all children experience are usually too mild to produce epilepsy. But epilepsy can result from head trauma severe enough to produce many hours of loss of consciousness or amnesia, penetrating injury of the brain or bleeding in the brain. A special exception is an immediate seizure from minor head trauma, for example, getting hit in the head by a soccer ball. This is called a concussive convulsion, and it rarely leads to subsequent seizures.

**Stroke**

We are increasingly recognizing seizures that occur for the first time in senior citizens. Our presumption is that many of these are a consequence of a brain injury from a previous stroke. During a stroke, brain cells die or are injured by blockage of blood flow to a part of the brain. About 10% of strokes lead to subsequent epilepsy. Some of these strokes may be so small as to have gone unnoticed, and may be detected only by a CT or MRI brain scan. Related to strokes is brain hemorrhage, which also can be an etiology for epilepsy. A seizure after a stroke does not mean that there has been another stroke.

**Infection**

Worldwide, infection is probably the most common cause for focal seizures. Organisms that can cause seizures include bacteria, viruses, fungi or parasites (most importantly cysticercosis, a microscopic worm from bad pork). If the bug infects the lining of the brain, the condition is meningitis. If the brain is infected, it is called encephalitis. Seizures may occur at the time of a brain infection or after a delay. Some of those viral “colds” or “flu’s” that we had in the past, with headache, fever and confusion, may have included brain infections, leading later to seizures.

**Vascular Malformations**

Abnormal blood vessels in the brain are common causes of epilepsy. Blood is brought to the brain by arteries. It flows into small capillaries, where oxygen is transferred to the brain cells, and then is carried out by veins. A malformation of arteries and veins is called an arteriovenous malformation (AVM). A malformation of capillaries is called a cavernous malformation or cavernous angioma. These malformations can be inborn or acquired after brain stresses, such as radiation. The brain cells near the malformation may be irritated by bleeding or lack of oxygen. The response to this irritation can be seizures.

**Tumors (Neoplasms)**

A brain tumor is a much-feared cause of seizures, but most seizures do not result from brain tumors. Brain tumors can be benign, malignant or sometimes in the borderland between the two. A common benign tumor is a meningioma (see figure), which grows from the cellophane-like lining of the brain and pushes on the brain, causing irritation and seizures. Tumors growing from brain include those named astrocytoma, oligodendrogliaoma, ganglioglioma, ependymoma and glioblastoma. A tumor that arises outside the brain can metastasize to brain.
Dysplasia

A dysplasia is a birth defect in the brain, consisting of abnormal but non-cancerous brain cells. Dysplasias are identified by MRI scans. Dysplasias do not grow or spread, but for unclear reasons, onset of seizures can be delayed until much later in life.

Mesial Temporal Sclerosis

This term literally means “inner temporal lobe scarring.” It shows on an MRI as a small bright hippocampus, which is a seizure-prone structure in the inner temporal lobe. MTS commonly is associated with complex partial seizures. Researchers debate whether MTS is a cause or a consequence of seizures. MTS can develop on the left, right or both sides of the brain. When only on one side, it may suggest the possibility of a surgical cure for the epilepsy, provided other testing confirms seizure origin from the region of MTS.

Causes for Generalized Seizures

Generalized seizures result from brain cell networks on both side of the brain being activated apparently at once. Unlike focal seizures, no one place in the brain can be identified by neurological exam, EEG or MRI as being abnormal. Causes for generalized seizures fall into three broad categories.

Metabolic

A wide variety of medical conditions can cause generalized seizures. As just a few examples, we can list low oxygen, low blood sugar, low blood sodium, low blood calcium, alcohol or sedative medication withdrawal, certain recreational or prescription drug overdoses, kidney or liver failure, hyperthyroid disease and toxemia of pregnancy. Enzyme deficiencies, often on a genetic basis, are important causes of seizures in young children. Metabolic causes produce seizures, but not epilepsy, since the seizures result from an immediate provoking factor, namely the metabolic derangement.

Medication Reactions

You should be aware that certain over-the-counter or prescription drugs can provoke seizures in people who are susceptible. A partial list of such medications includes: antihistamines (but not Claritin or Allegra, which do not get into the brain), ciprofloxacin (Cipro), metronidazol (Flagyl), tricyclic antidepressants (Elavil, Norpramine, amitriptyline, nortriptyline), clozapine (Clozaril), lithium (Lithobid), bupropion (Wellbutrin or Zyban), haloperidol (Haldol), Thorazine, Stelazine, high-dose meperidine (Demerol), some cancer chemotherapy agents, digoxin (Lanoxin), bromocriptine (Parlodel), verapamil (Calan), theophylline (aminophylline), tramadol (Ultram). This list is far from complete. If you need one of these medicines, you may still be able to take it, but let your doctor know that you have a seizure condition. Avoid over-the-counter remedies containing phenylpropanolamine or ephedrine (Ephedra, Ma-Huang).

Idiopathic (cause unknown)

Idiopathic seizures are those whose cause is unknown. Unfortunately, about 60% of all seizures are idiopathic. In the case of focal seizures, we presume that there is an irritation to or scar on some part of the brain, but the scar is invisible to MRI. With generalized seizures, the genetic or metabolic abnormality is unidentified. Patients and families are mystified by the absence of answers, typified by the common refrain: “The doctor’s told me everything was normal.” As frustrating as this may be, two points should be reassuring. First, no tumor, stroke, infection, vascular malformation or other problem was found. Second, we do not need to know the cause to use medicines to treat the seizures. As MRI and other forms of imaging the brain continues to improve, more and more causes of seizures will be identified.

Genetic Causes of Seizures

Scientists and clinicians increasingly recognize the importance of genetic factors in the origin of epilepsy. Genetics are most relevant to generalized seizures, including absence, generalized tonic-clonic, and myoclonic seizures. Defects in genes do not lead directly to epilepsy, but they can alter the excitability of brain in a way to predispose to seizures. Development of epilepsy can require multiple gene abnormalities, or a gene abnormality in concert with an environmental trigger. Hundreds of gene defects
eventually will be related to epilepsy. Only a few of these are now recognized, but this is one of the fastest growing areas of medicine. When we have a better picture of the genetic predisposition for seizures, pharmaceutical companies and "gene therapists" will be able to design anti-epileptic medications targeted to these deficits.

Parents with epilepsy worry whether their children will have epilepsy. The answer usually is no, but their children are at higher risk than baseline, particularly if the mother has a generalized type of epilepsy, in which case hereditary risk is about 5-20%.

Photosensitive Seizures

Many games, TV programs and public displays or events involve flashing lights that can provoke seizures in susceptible individuals. I had the opportunity to participate in the formulation of consensus opinions of experts on photosensitive seizures, under the sponsorship of the Epilepsy Foundation of America. These consensus opinions were published in the scientific journal Epilepsia a few years ago (2005, volume 46, issue 9, pages 1423-1425) but these are in a technical format. Here are some non-technical summary facts about photosensitive seizures and what you can do to avoid them.

A photosensitive seizure is defined as a seizure produced by flashing lights or certain visual patterns, for example moving stripes. About 3% of people with epilepsy overall will have photosensitivity that can be seen in their brainwave pattern (electroencephalogram or EEG) when lights are flashed. Not all people who have photosensitivity in their EEG will actually have a seizure in real life from flashing lights. Among an unselected population of all people in the community, about 1 in 10,000 adults and 1 in 4000 children might actually have a seizure sometime from flashing lights. Therefore, the population risk is low, but if you are susceptible, it can happen to you.

Photosensitive seizures can happen in people who do not even know that they have a seizure tendency, until it occurs. Light stimulation can provoke seizures, but it does not create epilepsy. Epilepsy is the tendency to have spontaneously recurring seizures, which is built into the characteristics of the person with epilepsy. Flashing lights simply provoke seizures in susceptible individuals.

The most common stimulus that can provoke a seizure is bright light flashes at frequencies between 10 and 25 flashes per second. Some people are susceptible to flash frequencies as low as one per second and some as high as sixty per second. The light must be bright and close enough to fill a large part, at least 25%, of the person's visual space. White light flashes are usually brightest, but some people are particularly susceptible to red light flashes or alternation between red and blue flashes. Such red and blue flashes in the so-called "rocket launch sequence" of a Pokémon cartoon in 1997 sent about 700 Japanese schoolchildren to the hospital with immediate seizures or other reactions. Some photosensitive individuals react more to patterns than to flashing lights. Vertical moving stripes, or moving dots may bring on a seizure. This can happen with light coming through window blinds or shimmering on a water surface.

Three common sources lead to possible photosensitive seizures: the environment, television and video games. An example of seizures from the environment would be sunlight flashing through rows of trees as you drive by. Faulty fluorescent lighting that flickers visibly or intentionally flashing lights in a discotheque are other environmental examples. Flashing fire alarms can provoke seizures, but the flash frequency has been reduced to less than three per second, so this is now unlikely. Television can provide flashing in two ways. One is the flickering of the picture itself, and the other is flickering of content that is shown on TV programs. Because of highly publicized television-induced seizures in Japan and the United Kingdom, these countries now screen video broadcast material for a potential to provoke seizures. No systematic method to do so is currently used in the United States, although individual studios and broadcast networks have their own safety screening programs. Flashing scenes in movies have not been as much of a problem because movies are overall darker than TV pictures.

Video games are harder to regulate than are TV broadcasts because people can play the game in so many different ways. If you make a character jump up and down in front of the sun it may produce repetitive flashing while playing the game. It is impossible to prescreen every pathway that someone might take while playing a particular game. The major video game manufacturers are aware of the potential of videogames for producing seizures. They provide warnings for susceptible individuals and work with videogame content creators to minimize the chances that a game could provoke a seizure. But that risk cannot be reduced to zero, except by not playing the game.

What can a person with epilepsy or parent of a child with epilepsy do to minimize the risk of a photosensitive seizure? One possibility is to eliminate videogames and TV. But the majority of children with epilepsy do not have seizures when playing video games or when exposed to flashing lights or patterns. Safety of particular games or TV shows can be known from personal experience or from testing the child with bright light flashes during recording of an electroencephalogram. Children who are not known to be susceptible to photosensitive seizures probably shouldn't have to endure the additional stigma of avoiding videogames, when all their friends are playing them. This has to be an individual decision made
among parent, child and the child's physician. Here are some reasonable general precautions:

1. Avoid bright flashing lights in the frequency range 10-25 per second. Look away or cover your eyes when exposed to such flashes. Covering one or both eyes is more effective than is closing the eyes, since bright flashes often penetrate the closed eyelids. Avoid playing video games that have precipitated seizures in the past.

2. Sit back at least 2 m (about 6 feet) from the TV screen or videogame screen.

3. Play in a well-lighted room so the contrast of the TV or videogame with background lighting is not too high.

4. Playing a videogame with one eye covered, for example by an eye patch, is useful to avoid light-induced seizures.

5. Take breaks from game-playing, with no more than one hour straight playing at a time, followed by a 15 minute break. Avoid playing when very tired, or when first arising in the morning, because these are more likely times to have a seizure.

Do not overreact with blanket prohibitions that may be unnecessary for a particular person. As with so many things pertaining to epilepsy, know what is safe for yourself or your child and guide your behavior accordingly.

**Medical Imitators of Seizures**

Not everything that looks like a seizure is a seizure: there are many look-alike imitators. The first question I consider when someone is referred to my clinic for seizures is whether they are in fact having seizures. Oftentimes, they are not. Patients have come to me for epilepsy surgery who did not have epilepsy. Others have been referred for adjustments of antiepileptic medication regimens of decade’s duration, with no evidence that the person had seizures in the first place. An open mind as to the diagnosis can have dramatic benefits.

Seizures come in many different types and therefore a wide variety of medical, neurological and psychological conditions can imitate seizures. A useful way to categorize imitators is by the presentation of the main symptom. Seizures can present with sudden loss of consciousness, intermittent confusion or abnormal movements.

**Loss of consciousness:** The start of a loss of consciousness episode may not be observed, and when the person is found unconscious, the question arises: was it a seizure? The most common cause for loss of consciousness is fainting, for which the medical term is syncope. Syncope results from sudden reduction of blood flow to the brain, either because of a blockage in circulation, blood loss, dehydration, or the blood rushing to and pooling in the muscles. Some people who faint will have a few jerks of their arms and legs as a response to the brain’s low levels of blood and oxygen. This is called convulsive syncope and is not epilepsy. Fainting can reflect a problem with the heart’s ability to pump blood adequately because of heart failure or an abnormal heart rhythm. This is a serious condition that should be evaluated immediately.

A warning stroke or transient ischemic attack (TIA) can lead to loss of consciousness. Like fainting, a TIA results from decreased blood flow to the brain. A TIA, however, restricts blood flow to a particular region of the brain fed by one or a few blood vessels. If the blood loss is in a critical area such as the brain stem, consciousness may be lost. TIAs may result from transient blood clots (emboli) or lasting circulation blockages in blood vessels to brain. Making a correct diagnosis and instituting treatment could prevent a serious stroke.

Extremely low blood sugar, a medical condition called hypoglycemia, can result in loss of consciousness. People usually experience lightheadedness, hunger, sweating, nausea and other physical symptoms before losing consciousness from hypoglycemia. The hypoglycemia can either be from inadequate food or from a high carbohydrate meal, which then provokes the pancreas to release too much insulin, resulting in low blood sugar.

Head trauma can produce loss of consciousness. Since head trauma also may cause amnesia, the person experiencing the trauma may not remember the blow to the head. If a person is found on the ground unconscious, with a bruise on the head it may be unclear whether the person first lost consciousness and then fell, or fell and then lost consciousness. Drug or alcohol intoxication is another cause of loss of consciousness that might be confused with seizures.

**Confusion episodes:** Many conditions can produce intermittent confusion. A TIA, described above, can produce confusion or speech problems without leading to full loss of consciousness. This may be mistaken for a seizure. Seizures usually last seconds to minutes and TIA’s minutes to a few hours, but the time course of each overlaps. TIAs do not produce rhythmic jerking or twitching, but seizures can. Several types of sleep disorders may be confused with seizures.

Narcolepsy is a condition of uncontrollable sleepiness. Sleep apnea interferes with breathing at night and causes a person to be very sleepy during the daytime. Bad sleep habits or shift-changing work may also produce excessive daytime sleepiness. When a person falls asleep inappropriately, they may be thought to be having seizures. Questioning will
reveal the irresistible sleepiness before each of the episodes. The person inappropriately asleep may be awakened, which is not true for a person in the midst of a seizure. Another symptom of narcolepsy is the condition known as cataplexy, in which a person will suddenly fall to the ground when startled or emotionally agitated. This is the origin of the old phrase "getting weak at the knees." It is not a seizure.

Migraine headaches sometimes produce periods of confusion, numbness, tingling and other neurological symptoms as part of the headache syndrome. When the headache is not as prominent as are these other symptoms, then diagnosis of a migraine can be difficult. This is particularly true since many people have headaches after their seizures.

During the condition known as transient global amnesia (TGA) a person suddenly becomes unable to register new memories. They will repeat the same questions over and over, never learning the answers. Old memories are preserved. Duration typically is a few hours, longer than the typical seizure. No other neurological functions besides recent memory are impaired during TGA, also distinguishing it from seizures, where more widespread impairment of mental functions tends to be the case.

Physicians diagnosis a condition called encephalopathy, which refers to globally poor functioning of the brain due to a medical cause. The cause might be a brain infection, low oxygen, abnormal electrolytes, toxicity from medications or recreational drugs, brain dysfunction from seizures, or one of many other possible medical causes. Encephalopathy waxes and wanes. The intervals of poor function may be mistaken for seizures, although the start and finish of the confusion is rarely so clear in encephalopathy as in a seizure.

Abnormal movements: Abnormal movements are produced when seizure activity involves the motor centers of the brain. Possible movements during a seizure include stiffening of a limb, grimacing, crying out, twitching/jerking of a limb and loss of muscle tone. Many types of movement disorders can resemble the movements occurring during a seizure, but movement disorders are not associated with EEG (brainwave) changes. A limb tremor that comes and goes can be mistaken for a motor seizure. A tic is a semi-voluntary twitching movement of a limb, eyelid or part of the face. It usually occurs a few times and then stops. With effort, it can be controlled, but at the expense of building up emotional tension and more vigorous tics when the control is relaxed. Chorea is a type of fidgeting, usually with the hands. Athetosis, which in Greek means swimming, indeed looks like swimming or writhing movements of the arms. Chorea and athetosis can be seen in neurological conditions such as Huntington's chorea, Sydenham's chorea from streptococcal infections, chorea of pregnancy (chorea gravidarum), as well as a toxic reaction to drugs. Dystonia refers to an abnormal sustained posture. The head may be twisted to the side or an arm may be stiff, for periods of seconds or minutes. Dystonia is a confusing symptom, even to doctors, because it can be a symptom of several movement disorders, but also part of a true epileptic seizure.

All three presentations of possible seizures - loss of consciousness, confusion and abnormal movements - can also be produced by the psychological imitators of epilepsy. That will be the subject of a future column.

How can your physician know that you truly have epilepsy, the condition of spontaneously recurrent seizures, and not one of the imitators? First, the physician must have an open mind to considering other diagnoses. Second, the doctor must have available, if at all possible, a detailed description of the nature of your episodes. This description should include what you subjectively feel during an attack, and what others observe you to do. Such a description may, for example, make it clear that you fainted or fell asleep. It is important how you felt leading up to the episode, what exactly you did during the episode, and the nature of the aftermath. What were the conditions that brought it on? Fasting might provoke hypoglycemia or fainting, but probably not a seizure. Seizures should have a relatively clear start and finish and last seconds to minutes. Many of the imitators exceed these boundaries. Third, medical testing can be helpful.

An EEG can disclose abnormal electrical activity of a type correlated with having seizures. But an abnormal EEG study never rules out seizures occurring at other times. An MRI or brain CT scan may show a structural abnormality of a type known likely to produce seizures. Fourth, response to antiepileptic medication may be diagnostically useful. Unfortunately, it may not, because some seizures do not respond to antiepileptic medications and many other conditions, such as depression, headaches, movement disorders and nerve-related pain, may respond to seizure medicines. A clinician experienced in seizure disorders, such as a neurologist or a neurologist with special expertise in epilepsy, known as an epileptologist, can best put the history, exam and test findings in the best context to come up with a correct diagnosis. In most cases, a diagnosis of epilepsy is fairly straightforward. If your seizures are not responding the way you and your doctor think they should, either they are intractable seizures (see prior column) or they are not seizures at all. It may be time to rethink the diagnosis.

Psychological Imitators of Epilepsy

While many medical conditions can be confused for epilepsy, the most difficult to differentiate are those that mimic the psychological aspects of a seizure. Some conditions affect the mind in a way that produces symptoms similar to seizures and can provide real diagnostic difficulties for doctors.
One such psychological imitator, called the breath-holding spell, is a type of episode that occurs in childhood. In a breath-holding spell (BHS) a child appears to hold his or her breath, becomes pale or blue, and then, if severe, loses awareness. It is a reflex, involuntary act, although it may result from a voluntary or semi-voluntary act causing the child to become emotional. Typically, a BHS begins with a provoking event, such as frustration, surprise, anger or fear. Crying or whimpering ensues and then pauses, at which time, a facial color change is evident. If the episode persists, the child will become poorly responsive, and may lose consciousness, becoming limp and falling. The term “breath-holding” causes confusion, as it may suggest that children hold their breath on purpose. This is not the case. Breathing may stop in some BHS, but the children do not hold their breath voluntarily. The cause of BHS is not known. Some attacks result from hyperactive normal reflexes, such as slowing of the heart rate when the eyes are rubbed, or when the child tries to breathe or scream against a closed throat (the Valsalva response). The children may have hyperactivity of the normal protective responses that the body automatically activates when oxygen levels begin to fall.

Prognosis of BHS is very good, but it must be said that rare cases of injury have been reported. Treatment consists of reassurance, and recognition that the episodes are rarely in the child’s control. Ultimately, time solves the problem, since breath-holding spells are outgrown by mid-childhood.

A night terror is another common condition that mimics epilepsy. It is seen most often among children aged 2 to 6. During the night terror, children will let out blood-curdling screams during sleep. The children rarely remember the episodes, but the parents do. While the breath-holding spells and night terrors can be frightening, they are generally benign, and not epilepsy.

On occasion, panic and anxiety can lead to episodes that mimic seizures. With anxiety can come hyperventilating, which is essentially breathing fast at a rate in excess of what the body needs. Excessive breathing may lead to low levels of carbon dioxide in the blood. This causes dizziness, numbness and confusion and may appear similar to symptoms of seizures. Hyperventilating may be the result of pain, anxiety or a panic attack. Once diagnosed, panic attacks can generally be controlled with a combination of medication and psychological care.

One especially confusing psychological imitator of epilepsy is called a psychogenic nonepileptic seizure or PNES. A PNES is a seizure-like event that is caused by psychological factors. Generally, the person experiencing a PNES is not aware of these factors and cannot control them. PNES do not come from electrical discharges of the brain, as do epileptic seizures.

A psychogenic nonepileptic seizure (PNES) is a seizure-like event that is produced, not by abnormal electrical charges in the brain, but by psychological factors of which the patient is not fully aware and cannot control. Psychogenic nonepileptic seizures go by many names, including pseudoseizures, psychological seizures, psychosomatic seizures, psychogenic seizures. Because thoughts and feelings have impact upon our physical being, unresolved stressors often manifest as physical symptoms, be they headaches, ulcers, skin rashes or shaking and blackouts that look like seizures. Sometimes the stressors that lead to a PNES involve extreme pressure to succeed in an area of one’s life. Other times, stressors are consequences of mental, physical or sexual abuse. These traumas can remain from years past, even dating back to childhood. The unconscious brain does not treat time in the same way that the conscious brain does, and old psychological issues can live on. They are even more potent if something happens today to bring back the feelings of yesterday. Therefore, a psychogenic nonepileptic seizure may result from unresolved stress and psychological tension dating back years.

It’s important to note that people with epileptic seizures list stress as one of the most common provoking factors. This means that having an event that is provoked by stress does not necessarily mean that the person is having a PNES. Family and friends of people with psychogenic nonepileptic seizures should realize that the person having the problem is not “faking,” it on intentionally, but that it is an involuntary medical condition. People with PNES are a very mixed group. Some have mental disorders such as depression, adjustment disorders, personality disorders or rarely even psychotic disorders. Then again, other people with PNES have no obvious underlying mental problems whatsoever. That’s why everybody needs to be evaluated and treated individually.

During the psychogenic nonepileptic event, the brain’s electrical activity, which is shown by its EEG pattern, remains normal. This point can be confusing even to doctors, because an EEG occasionally can be normal during epileptic seizures as well. Also, remember that the EEG is often normal between seizures in people who do have epilepsy.

On occasion, a person can have both nonepileptic and epileptic seizures, making diagnosis even more difficult. To those who have them or see them in a loved one, nonepileptic seizures are as real as are epileptic seizures. Any seizure-like event requires appropriate diagnosis and medical care.

Psychogenic nonepileptic seizures or PNES’s are complicated because, while they look like seizures, PNES’s do not result from abnormal electrical discharges in the brain. Instead, they are dictated by psychological events, which a
patient cannot control. Effectively diagnosing PNES’s begins with the physician considering the possibility that a person’s seizure-like events may not be epileptic seizures. By listening to a careful description of the events or looking at a home video of the episode, an experienced doctor can tell whether the attack has the characteristics of an epileptic seizure. But even experienced epilepsy specialists can be fooled by descriptions alone. An accurate diagnosis often can be made by recording the episode with a video and an EEG in an epilepsy monitoring unit. In cases where the patient's history is unclear and the event cannot be recorded, then the diagnosis may remain uncertain.

Once a diagnosis of PNES’s is made, treatment is very specialized and ideally should involve a partnership among a psychiatrist, a neurologist and the patient's primary care physician. However, not all psychiatrists and neurologists are familiar with psychogenic nonepileptic seizures. You can find physicians who are by contacting an epilepsy center at a university medical center near you.

When a patient finds the right treatment team, the treatment must be individualized because everyone is unique. Psychotherapy can be useful to help a patient explore, understand and manage the stressors that led to PNES’s. Patients also can train themselves to use relaxation exercises and mental imagery of a pleasant relaxing scene at the start of their events, in order to make them less intense.

Treating PNES’s is often complicated, because many patients with the condition are given heavy doses of antiepileptic medications. In the absence of epileptic seizures, these medications just produce side effects and make life even more difficult. Of course, remember that you should never stop taking a medication on your own. Work with your physician, because sudden withdrawal can be dangerous.

If someone in your family experiences PNES’s, try to keep calm, be quietly reassuring, and remember that a psychogenic nonepileptic seizure does not harm the brain. If there is thrashing or physical activity, you should protect from injury, but if your presence seems to prolong the attack it may be best to leave the person alone. In the long-term, you can help by encouraging participation in psychiatric care and their relaxation exercises.

A person having ongoing PNES is generally not safe to drive. After the episodes are controlled this can change, although caution is needed. The good news is that over half the people who experience psychogenic nonepileptic seizures can become episode-free. However, this prognosis depends upon the patient's motivation, how severe the underlying psychological or physical disorders are, and whether good medical help can be obtained.

If you or someone close to you is having either epileptic or psychogenic nonepileptic seizures, please contact a physician.

**Circumstances that Provoke Seizures**

Most seizures come “out-of-the-blue”, without rhyme or reason. However, some people with epilepsy list factors that contributes to their seizures. These possible factors include: missing seizure medications, times of the menstrual cycle in women, pregnancy, flashing lights, TV or video games, missing sleep, general physical illness, migraine headaches, rarely certain sounds, foods, sensory inputs or changes in temperature. Many people list stress as a provoking factor for seizures, but this relationship is inexact. Stress is everywhere, and most of the time it does not provoke seizures. Why some stress does, and some does not, provoke seizures is unknown.

Alcohol and alcohol withdrawal are common triggers for seizures, as is withdrawal from barbiturates (phenobarbital, Seconal, Nembutal, Mysoline) or benzodiazepines (Valium, Klonopin, Ativan, Tramxene, Librium, Xanax). Commonly used medications or drugs that can lead to seizures in susceptible people include: stimulants such as cocaine or diet pills, antihistamines (the prescription anti-histamines, Allegra and Claritin, do not provoke seizures), certain asthma medications (aminophylline), antidepressant medications (amitriptyline and related drugs), major tranquilizers (Thorazine, Haldol, Mellaril, Stelazine and relatives), certain pain medicines (Ultram, high-doses of Demerol), and some antibiotics (Flagyl, Cipro, Floxin, and others). No scientific evidence documents that caffeine, cigarettes, or Nutra-Sweet (aspartame) causes seizures, but a few people claim individual sensitivity. People report individual and highly unusual provoking factors, for exam-
ple, a certain type of smells or specific kinds of music, or the thinking of certain thoughts. Most seizures do not have provoking factors, and some factors are falsely blamed due to coincidence.

Tests for Epilepsy

The most important diagnostic test in epilepsy is a careful history, taking detailed information on the nature of the patient’s episodes. To an experienced clinician, the events should sound like seizures. The physician will then perform a physical and neurological examination looking for evidence of brain injury that might give a clue as to the cause and location of the seizure focus. In epilepsy, however, the history is usually more important than the physical examination.

Blood tests will be done to look for infectious or chemical causes of seizures, such as low blood sugar, low blood calcium, low oxygen, kidney failure or liver failure, or drugs or toxins in the blood. Blood tests are also important as a baseline if antiepileptic medications are to be used, since they indicate baseline normality of white blood counts, red blood counts, platelets, liver and kidney function.

The physician may get an x-ray of the brain to see if there is an underlying structural cause of the seizures such as tumor, blood clot, or abnormal blood vessels, abscess, old stroke, or other structural causes. A magnetic resonance imaging (MRI) scan is more detailed and useful for seizure diagnosis than is the older CT scan, but individual doctors may choose one over the other. If there is any question of infectious meningitis causing the seizure, then a physician may perform a lumbar puncture (spinal tap) to rule out this condition.

The electroencephalogram (EEG) has special importance in the diagnosis of epilepsy. The EEG measures electrical activity of the brain. Normal brain electrical patterns can be recognized by experienced electroencephalographers.

During a seizure the brain shows a high voltage rhythmical pattern of activity, which is a little different for each seizure type. The abnormal electricity appears in a certain region of the brain which can give a clue to what part of the brain has the seizure focus, or place of origin. The EEG can also help classify the type of seizures. EEGs would not be very useful if they required recording during a seizure. Fortunately for diagnosis, 50-80% of individuals have some abnormal EEG patterns, called spikes, in between seizures. These are brief high voltage discharges in the EEG which may mark a tendency for seizures and a place where seizures originate. Patients do not have much in the way of symptoms from spikes because they are so brief. Such spikes are also called interictal spikes, because interictal means between seizures. Absence (petit mal) seizures have a pattern known as spike-waves with spikes and after going slow waves.

There are a few important things to know about EEG. First, EEG never makes a diagnosis of epilepsy. It is only an adjunctive test to support a clinical history which is consistent with epileptic seizures. Some people may have abnormal spikes in their EEG but never have a seizure and should not be diagnosed as having epilepsy. Second, the EEG may be normal between seizures in people with epilepsy. If a patient has a good story for seizures, a negative EEG should not discourage the clinician from treating the patient for those seizures. Therefore, the EEG is helpful as additional information to secure a diagnosis of epilepsy, and to classify and localize the type of seizures.

Sometimes it is important to record behavior and EEG during a seizure. In this case a patient may undergo inpatient video-EEG monitoring. In such a procedure the EEG is left attached for several days to the patient who can wander freely around the room on a cable. A TV camera records behavior. Medications may be discontinued to provoke seizures for analysis. The most important thing to learn from this is what type of electrical activity is present at the start of a seizure and where in the brain it occurs. Such video-EEG monitoring is done in patients who are being evaluated for possible curative seizure surgery. Video monitoring may also be done in patients where there is a question as to whether the patient is suffering from epilepsy or one of the imitators of epilepsy (see below).

During a seizure, the EEG demonstrates a rhythmical build-up of electrical activity (Fig. 7). The place at which this activity begins can help to identify the seizure focus. Unless seizure activity is very frequent, a prolonged EEG recording session may be required to capture a seizure. Fortunately, diagnosis and treatment with medicines (as opposed to surgery) usually does not require recording of a seizure.
Absence (petit mal) seizures have a pattern known as “spike-waves” with spikes and after going slow waves (Fig. 6).

The EEG in isolation never establishes a diagnosis of epilepsy, since a few percent of the normal population has EEG spikes. A history of seizure-like events would be required to diagnose epilepsy. Contrarily, the EEG cannot rule out epilepsy, since EEG can be normal between seizures in people with epilepsy. If a patient has a good story for seizures, a negative EEG should not discourage the clinician from treating the patient for those seizures. Therefore, the EEG is an adjunctive test, helpful to add additional support to a diagnosis of epilepsy, and to help to classify and localize the type of seizures.

A clinician will refer a patient for specialized EEG testing when prolonged recording or correlation of EEG and behavior are required. Video-EEG monitoring is done in patients who are being evaluated for possible curative seizure surgery. Video monitoring may also be done in patients where there is a question as to whether the patient is suffering from epilepsy or one of the imitators of epilepsy (see below). In such a procedure, the EEG is left attached for several days to the patient who can wander freely around the room on a cable. A TV camera records behavior. Medications may be discontinued to provoke seizures for analysis. The most important thing to learn from this is what type of electrical activity is present at the start of a seizure and where in the brain it occurs. Ambulatory EEG monitoring also can be accomplished in the outpatient setting, with special cassette recorders.

Postictal: The Aftermath of a Seizure

The following quote is from a 22 year-old ski instructor with epilepsy.

For the following two days after that seizure, I just kinda feel out of it, although physically I continue with my daily duties. I cannot, for those two days, remember to call friends, to do things like I normally would, and I just kinda stay at home and perform things at home. The ideas don’t come in as fast as they normally would to do things. Energy level during those two days is way down. My mood is kind of just down and I kinda enjoy being by myself.
Definition: In the ancient Greek language, a seizure was called “ictal,” and so the time period after a seizure is “postictal.” For some people with epilepsy, the aftermath of a seizure is worse than the seizure itself. The seizure may last a minute, but the recovery to normal functioning can take hours or even days. The quote above illustrates three possible aspects of the postictal state: physical, cognitive (thinking) and psychiatric problems.

Physical problems are the most obvious. Tonic-clonic (grand mal) seizures often produce muscle soreness, bruises and other injuries, or a bitten tongue. Complex partial and other seizures can lead to headaches, dizziness, stomach upset and fatigue. A prolonged seizure in one part of the body, for example, the right arm, can leave that arm partly paralyzed for hours or days. This phenomenon is called Todd’s paralysis, after a 19th century British physician who described it. A seizure and resulting paralysis rightly cause patients, doctors and families to worry about an underlying stroke; yet, the temporary paralysis can result from a seizure alone, in which case it will have no lasting consequences.

Postictal thinking problems come on suddenly and resolve over time. In the immediate aftermath of a seizure, a person may not be able to speak, recognize his/her own name or follow instructions. Fortunately, this severe disability usually lasts only minutes. Then the person seems to be mentally recovered. But are they? A less obvious impairment of thinking may in fact continue for days. The head seems “fuzzy,” words are elusive, level of absent-mindedness is high. Some patients have likened it to having a hangover. For those who have prolonged postictal impairment of thinking, it must take a great effort to function well at work or school.

Postictal psychiatric problems are least often recognized. These include delirium, depression, mania and postictal psychosis. Postictal psychiatric symptoms can be very debilitating, even when temporary. Delirium is a condition of disorientation, sometimes with agitation and occasionally aggressive behavior. It is common immediately after a complex partial or generalized tonic-clonic seizure. Postictal depression is under-recognized. Brain chemistry changes produced by a seizure and affecting the system of neurotransmitters and receptors also contribute to postictal depression. The mood can be low for days. A component of postictal depression may be a reaction to problems caused by having the seizure, for example, suspension of driving, or the need to take more medicines. For poorly understood reasons, some people develop postictal hypomania, the opposite of depression. Mood may be inappropriately happy or excited, words and ideas, not all of which are logical, may come in a torrent. Sleep is near impossible. Beneath this increased energy often lies irritability and a temper on a short fuse. The mood may swing between depression and hypomania.

Postictal Psychosis: The most mysterious and troublesome seizure aftermath is a condition called postictal psychosis. In psychosis, a person is out of touch with reality, experiencing illogical thinking, sometimes paranoid suspicions, delusions (false ideas) or hallucinations (false perceptions, visions, sounds, voices, skin sensations or smells). Onset of a postictal psychosis is delayed for a few days after a seizure, providing a so-called “lucid interval.” Postictal psychosis typically persists for a few days to a few weeks. It can be treated symptomatically with antipsychotic medications, sedatives and lot of reassurance that it will go away.

As a rough estimate based on personal experience and review of literature, about 75 percent of people with seizures will experience postictal delirium, 50 percent some element of postictal depression, 10 percent postictal hypomania and 3 percent postictal psychosis.

What can be done? The first need is to recognize the existence of a postictal condition. You are not necessarily to blame for acting and feeling the way you do after a seizure. It is part of your medical condition. Second, know your own pattern, and adapt your routine to allow time for recovery. Don’t make that Grand Canyon climb right after a seizure. Take a break from work or school rather than turning in a befuddled performance. Third, get help from your medical team if you have injuries, ongoing pain, extreme or prolonged confusion (in this case, the seizures may not yet be fully over), or any symptoms of psychosis. So far, the treatment for postictal problems is symptomatic. We have no drug to safely and reliably reverse the condition, and this is a subject in much need of more research. Lastly, do your best to control your seizures: no seizures -- no postictal state.

The unintentional philosopher and baseball catcher, Yogi Berra, pointed out “It ain’t over till it’s over.” The effects of seizures may not be over for a long time.

MEDICATIONS FOR EPILEPSY

Most epilepsy specialists use several principles to govern the treatment of seizures with antiepileptic medications. These are listed in Table 3.

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRINCIPLES OF AED THERAPY</td>
</tr>
<tr>
<td>Decide whether to treat</td>
</tr>
<tr>
<td>Decide how long to treat</td>
</tr>
<tr>
<td>Use monotherapy where possible</td>
</tr>
<tr>
<td>Use simple regimens</td>
</tr>
<tr>
<td>Encourage compliance</td>
</tr>
</tbody>
</table>
Choose the best drug for a seizure type

This summary represents the opinion of the author, Dr. Robert Fisher, who is an epilepsy specialist, and it is not necessarily the official drug description that can be found in the package insert. No drug companies have paid for or reviewed these opinions. **DO NOT TRUST DRUG DOSAGES IN THIS DOCUMENT - Check with pharmacy or package insert sources!**

There is no formula to choose which seizure medicine to use for a particular patient. No one medicine dominates for effectiveness, and all have various side effects. Doctors and patients choose AEDs after considering which side effects should be avoided in particular cases, convenience of use, cost and physician experience. An important start is to know which AEDs work for which seizure types. The narrow spectrum AEDs mostly work for specific types of seizures (such as partial, focal, or absence, myoclonic seizures). Broad spectrum AEDs additionally have some effectiveness for a wide variety of seizures (partial plus absence myoclonic seizures). Some types of seizure are difficult to treat with any AED. (To learn what these seizure types are, see [http://www.epilepsy.com/node/3007](http://www.epilepsy.com/node/3007)).

Narrow-spectrum AEDs:  
- phenytoin (Dilantin)  
- phenobarbital  
- carbamazepine (Tegretol)  
- oxcarbazepine (Trileptal)  
- gabapentin (Neurontin)  
- pregabalin (Lyrica)  
- lacosamide (Vimpat)  
- vigabatrin (Sabril)

Broad-spectrum AEDs:  
- valproic acid (Depakote)  
- lamotrigine (Lamictal)  
- topiramate (Topamax)  
- zonisamide (Zonegran)  
- levetiracetam (Keppra)  
- clonazepam (Klonopin)  
- rufinamide (Banzel)

**General Points**

1. **Brand vs. generic.** Every medicine has a brand and a generic name. The generic usually is cheaper, sometimes by quite a lot. For medicines introduced in recent years, patent (or “market exclusivity”) protection may block the sale of generic versions. A generic medicine usually works well, but it may not generate the same blood levels as does the brand name or an alternative generic medicine. Therefore, with changes of pill manufacturers, the blood levels can change. This may produce breakthrough seizures or side effects. The most important concern when taking generic drugs is to be sure the tablets are made by the same manufacturer for each refill. Switching from one generic manufacturer to another could result in different amount of active drug in each pill. The current author supports the right of the patient and doctor to know about medication substitution and consider whether generic substitution is safe.

2. **Starting schedule:** Many AEDs have to be started slowly to minimize side effects, even though this delays helping the seizures. The titration (starting) schedules are those of the author, and may be slower than is the schedule recommended in the package insert. Dosages are all for adults. Children are treated on the basis of their weight (mg per kg dosing basis).

3. **Monotherapy:** Some AEDs have approval for monotherapy (to be used alone) and others only as adjunctive (add-on) therapy to another AED. This reflects what testing evidence has been presented to the FDA - not all AEDs have gone through the required two clinical studies to show effectiveness in monotherapy. AEDs not proven effective in monotherapy still probably work well as single medications and are used that way by epilepsy doctors on a case-by-case basis where the benefit seems to exceed the risk.

4. **Blood levels:** Target blood levels are broad guides to clinical use. Actual blood levels differ for different laboratories. The desirable level depends upon the type and number of seizures, side effects, taking one vs. multiple drugs and other clinical factors.

5. **Side effects:** Side effects listed below are a brief compilation of the most common and most worrisome, not a full list. Every seizure medicine can sometimes cause side effects of fatigue, dizziness, unsteadiness, blurry vision, stomach upset, headaches, reduced resistance to colds, memory and thinking problems. Weight gain tends to occur with valproic acid (Depakote), gabapentin (Neurontin), pregabalin (Lyrica) and carbamazepine (Tegretol, Carbatrol). Weight loss tends to occur with topiramate (Topamax), zonisamide (Zonegran) and felbamate (Felbatol). These are not mentioned separately in each section, unless they are especially common with the medicine. Detailed information is provided by the pharmacy as a package insert for new prescriptions and refills.

6. **Effects on internal organs:** All seizure medicines can cause problems with blood counts (white cells, red cells and platelets), or liver or other internal organs, so doctors usually order blood tests to screen for these problems. Blood can be tested when starting a medicine to get a baseline, after a few months on the drug, every few months to yearly thereafter, then at individually determined times. The package insert often has recommendations, but there are no universal rules about when to test blood. All seizure
medicines can produce either mild or severe allergic reactions. One, called the hypersensitivity syndrome, produces fever, rash, fluid accumulation, swollen lymph nodes, possible liver injury and confusion

7. Suicide warning: The US FDA has required a suicide warning on all seizure medications as a general class. All people taking them should be aware of and report any serious depression or suicidal thinking to their doctor, but the actual risk for suicide due to AEDs is quite low.

8. Mechanism: Mechanisms of action in the brain for antiepileptic drugs are described in simple form: most AEDs have multiple mechanisms of action to block seizures.

9. Not a cure: Although AEDs are called “antiepileptic,” they do not cure epilepsy, but just suppress seizures while the medications are in the body.

**Brief Summary of Antiepileptic Drugs**

carbamazepine (brief)
(Tegretol, Carbatrol): A favorite partial seizure medicine in the developed world. Carbamazepine affects sodium channels, and inhibits rapid firing of brain cells. Long-acting forms such as Carbatrol or Tegretol-XR can be given once a day. Potential side effects include GI upset, weight gain, blurred vision, low blood counts, low blood sodium (hyponatremia). Carbamazepine causes a rash rate of a few percent, sometimes even the dangerous rash called Stevens-Johnson syndrome. People of Asian descent with HLA-B*1502 antigen are more at risk. Typical adult dose is 400 mg tid. I start my patients with 200 mg bid and each week, and increase by 200 mg daily to about 400 mg three times a day. See [http://www.epilepsy.com/medications/b_carbamazepine_intro](http://www.epilepsy.com/medications/b_carbamazepine_intro) and [http://www.epilepsy.com/medications/b_carbatrol_intro](http://www.epilepsy.com/medications/b_carbatrol_intro)

clonazepam (brief)
(Klonopin): Clonazepam is a member of the drug class known as benzodiazepines, to which diazepam (Valium), lorazepam (Ativan), clorazepate (Tranxene), alprazolam (Xanax) also belong. Benzodiazepines are used as anti-seizure drugs, sedatives, tranquilizers and muscle relaxants. Benzodiazepines increase the effectiveness of GABA, the brain’s main inhibitory neurotransmitter. Clonazepam is more long-acting against seizures than are diazepam or lorazepam. Side effects of clonazepam include sedation, thinking/memory impairment, mood changes, addiction. More so than most, its effects wear off over time. A typical adult dose is 0.5-1.0 mg three times a day. I usually start my patients with 0.5 mg at night, and if they are not too sleepy the next day, increase to 0.5 mg twice a day. A week later, if seizures persist, I will increase to 0.5 mg three times a day. See [http://www.epilepsy.com/medications/b_clonazepam_intro](http://www.epilepsy.com/medications/b_clonazepam_intro)

gabapentin (brief)
(Neurotin): Gabapentin has the reputation of being a safe but not particularly powerful AED. The effectiveness criticism probably is because it is often prescribed at too low a dose. The drug probably works by influencing transport of GABA and effects on calcium channels. It has no drug interactions, is not metabolized in the liver and it does not bind to blood proteins. Side effects are unsteadiness, weight gain, fatigue, dizziness. Typical adult dose is 300-600 mg three times a, but doses can be up to 1200 mg three times a day. I often start at 300 mg per day, sometimes in one dose or with 100 mg pills, and increase over a month or two to the full dose. Gabapentin often is used also for chronic pains of certain types. See [http://www.epilepsy.com/medications/b_gabapentin_intro](http://www.epilepsy.com/medications/b_gabapentin_intro)

lacosamide (brief)
(Vimpat): Lacosamide is a new (2009) antiepileptic drug, for partial and secondarily generalized seizures. It is chemically related to the amino acid, serine. Vimpat blocks sodium channels (but in a different way from other seizure medicines), and this block reduces brain excitability. Side effects include dizziness, headache, nausea or vomiting, double vision, fatigue, memory or mood problems. Vimpat may affect the internal organs, blood counts or heart rhythm, but these potentially serious side effects are infrequent. The recommended starting dose is 50 mg twice daily, increased each week by an extra 100 mg, to the recommended maintenance dosage of 100-200 mg twice a day. See [http://www.epilepsy.com/medications/b_vimpat_intro](http://www.epilepsy.com/medications/b_vimpat_intro)

lamotrigine (brief)
(Lamictal): A broad-spectrum alternative to VPA, with a better side effect profile. However, LTG may not be as effective for myoclonic seizures. Lamotrigine works by several mechanisms including blocking release of glutamate, the brain’s main excitatory neurotransmitter. It has the usual side effects of dizziness and fatigue, usually mild cognitive (thinking) impairment. Severe medical side effects are unusual. The practical side effect issue is rash, occurring in 5-10% of people who take it, especially if the dose is increased too fast. Therefore, it takes a couple of months to get up to the typical adult dose of 200 mg twice a day. I usually start my patients at low doses, adding one 25 mg pill daily each week on a two-times-a-day schedule until taking 100 mg twice a day. If there is no rash at that time, one is unlikely. I then switch my patients to 100 mg pills and increase to 200 mg twice a day over the next few weeks. This is slower than the package insert suggested starting dose, however, a slow starting dose is especially important if the patient also takes valproic acid (Depakote), to reduce risk for rash. Lamotrigine is also used for mood stabilization. See [http://www.epilepsy.com/medications/b_lamictal_intro](http://www.epilepsy.com/medications/b_lamictal_intro)
levetiracetam (brief)
(Keppra): Levetiracetam is one of the more used medicines in seizure clinics because it probably is effective for a broad-spectrum of seizures types, has a relatively low incidence of causing thinking/memory problems, and can be started at 500 mg twice a day, which is an effective dose. It has no drug interactions, is not metabolized in the liver and it does not bind to blood proteins. The most common side effects are dizziness, fatigue, insomnia, but the more troublesome problem can be irritability and mood changes. This may occur to some degree in up to a third of those taking the medicine. A typical adult dose is 500 - 1500 mg twice a day. I usually start my patients with 250 mg twice a day and increase the next week to 500 mg twice a day, then the next week to 1000 mg in the am plus 500 mg in the pm, then the week after to 1000 mg twice a day. This is slower than the package insert suggested starting dose. See http://www.epilepsy.com/medications/b_keppra_intro

lorazepam (brief)
(Ativan): Lorazepam is similar to clonazepam in dosage and action, but it is not as long-acting. It is usually used as a ‘rescue medication’ for patients who frequently have clusters of seizures. It works reasonably quickly when taken orally and anti-seizure effect lasts for 2-6 hours. Typical adult dose is 0.5-2.0 mg orally or as needed. A lorazepam concentrate, 2 mg per ml, can be taken as 1 ml liquid under the tongue in urgent situations.

oxcarbazepine (brief)
(Trileptal): Slightly different from carbamazepine, it is at least as effective, and may have fewer side effects, except for more risk for low blood sodium (hyponatremia). It is more expensive than generic carbamazepine. A typical adult dose is 600 mg twice a day. I start my patients with 150 mg twice a day, and increase by 150 mg daily each week. This is slower than the package insert suggested starting dose. An immediate switch from carbamazepine to full-dose oxcarbazepine is possible in some cases. See http://www.epilepsy.com/medications/b_trileptal_intro

phenobarbital (brief)
(Luminal): The old-timer: very inexpensive and effective in a single daily dose. Phenobarbital increases the effect of GABA, the main inhibitory neurotransmitter in the brain. Watch for sedation, thinking/memory problems and depression. Phenobarbital can cause long-term bone problems. Phenobarbital is mildly addictive and requires slow withdrawal. During pregnancy, there is a significant rate of birth defects. Typical adult dose is around 100 mg per day. I start my patients with 30 mg pills, 2 or 3 at bedtime, to allow for future dosage flexibility. The target serum level is 10-40 mcg per ml. See http://www.epilepsy.com/medications/b_phenobarbital_intro

phenytoin (brief)
(Dilantin): The most used AED by general physicians in the US, less so by epilepsy doctors, because of the side effects. Phenytoin alters brain cell sodium channels, which has the effect of limiting rapid firing of the brain cells. It is inexpensive. Common side effects are unsteadiness and moderate cognitive problems. There are long-term potential cosmetic (body/face hair growth, skin problems), and bone problems (osteoporosis). Phenytoin causes a rash rate of a few percent, sometimes even the dangerous rash called Stevens-Johnson syndrome. Typical adult dose is 300-400 mg per day, usually with 100 mg pills. Phenytoin can be started quickly in an emergency with intravenous administration, or a large dose of capsules if an immediate effect is required. Small changes in phenytoin dose can cause large changes in serum drug levels, so the blood levels can be hard to regulate. The target serum level is 10-20 mcg per ml. See http://www.epilepsy.com/medications/b_phenytoin_intro

pregabalin (brief)
(Lyrica): A relative of gabapentin, it may be better, and can be given twice a day. Some believe that it is more effective against seizures than is gabapentin. Pregabalin has no drug interactions, no liver metabolism, no protein binding, and similar side effects to gabapentin. Typical adult dose is 150 - 600 mg bid. I usually start my patients with 50 mg daily, adding 50 mg each week on a twice a day basis until taking 500 - 600 mg per day. This is slower than the package insert suggested starting dose, but avoid sedation. Pregabalin often is used also for chronic pains of certain types.

rufinamide (brief)
(Banzel, Inovelon in Europe): Banzel is approved for add-on treatment of children age 4 and older and adults with the Lennox Gastaut Syndrome (see http://www.epilepsy.com/EPILEPSY/epilepsy_lennoxgastaut ). This syndrome can include seizure types such as atonic (drop) seizures, tonic (stiffening) seizures, myoclonic (brief jerking) seizures, or staring (absence) seizures, as well as partial seizures. Banzel works on sodium channels in brain cells, in a way to make them less excitable. Common side effects include headache, dizziness, fatigue and sleepiness, double vision and tremor (trembling). People who have the “short QT syndrome,” a rare heart rhythm irregularity, should not take Banzel. The drug comes as 200 and 400 mg tablets. Children will usually be started at doses of approximately 10 mg/kg/day administered in two equally divided doses. Dosing can increase by adding additional 10 mg/kg amounts every two days, until the child is taking 45 mg/kg/day or a maximum of 3200 mg/day, divided into two doses each day. See http://www.epilepsy.com/medications/b_banzel_intro

topiramate (brief)
(Topamax): A good broad-spectrum AED (i.e., treats all types of seizures). Topiramate has several mechanisms, including
blocking the enzyme carbonic anhydrase, which affects the acidity of brain tissue. More acidity (to a point) suppresses seizures. Side effects include thinking and memory problems in about 1/3rd, renal stones in 1-2%, rare cases of glaucoma (increased eye pressure) and weight loss. Typical adult dose is 150-200 mg twice a day. I usually start my patients with one 25 mg pill daily, adding another pill each week on a two-times-a-day schedule until taking 100 mg twice a day. If there are no significant side effects, I then switch my patients to 100 mg pills and increase to 200 mg twice a day over the next few weeks. Topiramate also is used for migraine headache prevention. See http://www.epilepsy.com/medications/b_topamax_intro

valproic acid (brief)  
(Depakote): This is the standard broad-spectrum AED (treats all types of seizures) and no other AED is more effective for generalized seizure types. VPA has effects on GABA (at least in very high doses), and a neurotransmitter called NPY to block seizures, and maybe also on calcium channels. VPA has significant side effects: weight gain, tremor, hair loss, GI upset, blood count decreases, hepatic or pancreatic injury, bone weakness over time (osteoporosis), birth defects in up to 10% (folic acid can help to prevent them). Typical adult dose is 250 mg - 500 mg three times a day, but dose can be higher. An extended release form can be taken once a day. See http://www.epilepsy.com/medications/b_valproacid_intro

vigabatrin (brief)  
(Sabril): Vigabatrin is a "designer drug," made to block metabolism of GABA, the brain’s main inhibitory neurotransmitter. Sabril has been used for over a decade in many countries, and it is effective for partial seizures, with or without secondary generalization. It also may be very effective for infantile spasms, a serious type of seizures in young children. Release in the US was delayed because the drug is toxic to the retina of the eye in up to 30% of people who take it long-term. This toxicity can result in permanent loss of peripheral vision. Regular vision testing is required for all people on this drug. A typical regimen begins with 500 mg twice a day, and can increase over a month or two to 1500 mg twice a day.

zonisamide (brief)  
(Zonegran): Zonisamide is rather similar in its coverage and side effects to topiramate, except glaucoma is not usually listed. Some find less cognitive impairment than with topiramate but this is individual and dose-dependent. Typical adult dose is 100-300 mg twice a day. I usually start my patients with one 25 mg pill daily, adding 25 mg each week on a two-times-a-day schedule until taking 100 mg twice a day. If there are no significant side effects, I then switch my patients to 100 mg pills and increase to 200 mg twice a day over the next few weeks. See http://www.epilepsy.com/medications/b_zonisamide_intro

others (brief)  
acetazolamide (Diamox), diazepam rectal gel (Diastat), ethosuximide (Zarontin), felbamate (Felbatol), primidone (Mysoline), tiagabine (Gabitril) can be searched individually on www.epilepsy.com.

ANTIEPILEPTIC DRUG SELECTION

Scientifically controlled comparative studies of seizure medicines are few. The most important of these are the two VA Cooperative Studies, which compared phenytoin, phenobarbital, carbamazepine, primidone, and valproic acid for treatment of simple partial seizures. Table 4 gives brand names and generics of the seizure medications. Carbamazepine and phenytoin are drugs of choice for partial seizures. Where cost is not a key factor, oxcarbazepine may be a good substitute for carbamazepine. Levetiracetam, pregabalin, topiramate, zonisamide and lacosamide all have activity against partial seizures. Valproic acid is a drug of choice for primary generalized seizures, but is slightly less effective than is carbamazepine for partial seizures. Nevertheless, most of the medications are close in efficacy. Medicines in this group can be chosen for ease of use, cost, side effects, and familiarity by the treating physician. Table 4 lists brand names and generic names for drugs used to treat seizures in the United States. Table 5 gives the opinion of the author about drugs useful for particular types of seizures.

Table 4: Drugs used to treat seizures

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ativan</td>
<td>lorazepam</td>
</tr>
<tr>
<td>Banzel</td>
<td>rufinamide</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>Celontin</td>
<td>methsuximide</td>
</tr>
<tr>
<td>Cerebyx</td>
<td>fosphenytoin</td>
</tr>
<tr>
<td>Depacon</td>
<td>VPA injectable</td>
</tr>
<tr>
<td>Depakene</td>
<td>valproic acid</td>
</tr>
<tr>
<td>Depakote</td>
<td>divalprox</td>
</tr>
<tr>
<td>Depakote-ER</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Diamox</td>
<td>acetzolamide</td>
</tr>
<tr>
<td>Diastat</td>
<td>rectal diazepam</td>
</tr>
<tr>
<td>Dilantin</td>
<td>phenytoin</td>
</tr>
<tr>
<td>Diprivan</td>
<td>propofol</td>
</tr>
<tr>
<td>Felbatol</td>
<td>felbamate</td>
</tr>
<tr>
<td>----------</td>
<td>------------------</td>
</tr>
<tr>
<td>Frisium</td>
<td>clobazam</td>
</tr>
<tr>
<td>Gabitril</td>
<td>tiagabine</td>
</tr>
<tr>
<td>Keppra</td>
<td>levetiracetam</td>
</tr>
<tr>
<td>Klonopin</td>
<td>clonazepam</td>
</tr>
<tr>
<td>Lamictal</td>
<td>lamotrigine</td>
</tr>
<tr>
<td>Luminal</td>
<td>phenobarbital</td>
</tr>
<tr>
<td>Lyrica</td>
<td>pregabalin</td>
</tr>
<tr>
<td>Mebaral</td>
<td>mephobarbital</td>
</tr>
<tr>
<td>Mesantoin</td>
<td>mephenytoin</td>
</tr>
<tr>
<td>Mysoline</td>
<td>primidone</td>
</tr>
<tr>
<td>Neurontin</td>
<td>gabapentin</td>
</tr>
<tr>
<td>Peganone</td>
<td>ethotoin</td>
</tr>
<tr>
<td>Phenurone</td>
<td>phenacemide</td>
</tr>
<tr>
<td>Sabril</td>
<td>vigabatrin</td>
</tr>
<tr>
<td>Tegretol</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>Tegretol-XR</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>Topamax</td>
<td>topiramate</td>
</tr>
<tr>
<td>Tranxene</td>
<td>clorazepate</td>
</tr>
<tr>
<td>Trileptal</td>
<td>oxcarbazepine</td>
</tr>
<tr>
<td>Valium</td>
<td>diazepam</td>
</tr>
<tr>
<td>Versed</td>
<td>midazolam</td>
</tr>
<tr>
<td>Vimpat</td>
<td>lacosamide</td>
</tr>
<tr>
<td>Zarontin</td>
<td>ethosuximide</td>
</tr>
<tr>
<td>Zonegran</td>
<td>zonisamide</td>
</tr>
</tbody>
</table>

The section below gives more details on individual AEDs, and is meant for reference, rather than reading. More information can be found in the package insert for each medicine: see [http://dailymed.nlm.nih.gov/dailymed/about.cfm](http://dailymed.nlm.nih.gov/dailymed/about.cfm) and enter drug name in the search box.

**Benzodiazepines:**

The benzodiazepines consist of the “Valium-like” drugs such as Valium itself (diazepam), Klonopin (clonazepam), Ativan (lorazepam), Tranxene (clorazepate), alprazolam (Xanax), clobazam (Frisium). These medicines are effective as quick-acting antiepileptic medications that work within minutes to hours, and do not require a loading dose. Therefore, injectable forms such as intravenous diazepam or intravenous lorazepam are typical drugs of choice for treatments of status epilepticus. Used chronically, their effectiveness tends to wear off after a few weeks of use. In addition, increasing doses are sometimes required. Chronic use of benzodiazepines usually is discouraged, with the exception of treatment for atonic, myoclonic or completely intractable seizures, where few alternatives exist. Benzodiazepines can be useful as booster therapy for clusters of seizures, taken for a single dose or a day or two. This can happen when individuals know one seizure is likely to lead to another, or at times like the menstrual period for women. A typical dose of diazepam (Valium) would be 2-5 mg every 4-6 hours for seizures. Clonazepam (Klonopin) usually is given as 0.5-2.0 mg orally three times per day. Ativan may be given in 0.5-1.0 mg boosters, repeated as needed to stop seizures up to about 4 mg per day.

Be aware of the sound-alike drug, clonidine, a blood pressure medicine, sometimes mistakenly substituted for Klonopin!

A rectal gel form of diazepam, called Diastat, is designed to be given for clusters of seizures ("serial seizures"). The rectal gel can be administered when swallowing pills is not possible. The gel is absorbed rapidly from the rectal mucosa. Diastat comes packaged in adjustable dose syringes without needles, in doses of 2.5, 5, 10, 15, 20 mg. The usual adult does is 0.2 mg/kg (5-20 mg). Pediatric dose is 0.5 mg/kg for ages 2-5 and 0.3 mg/kg for 5-20 years. Maintenance is not relevant, since Diastat is an acute rescue medicine. However, the dose may be repeated once in 4-12 hours.

**Summary data for BDZs**

Pill sizes: Klonopin 0.5, 1, 2 mg; Ativan 0.5, 1, 2 mg; Valium 2, 5, 10 mg pills; Tranxene 3.75, 7.5, 15 mg pills; Tranxene slow release 11.25, 22.5 mg pills.

Liquid for oral: Valium solution 5 mg/ml

Injectable: Valium 5 mg/ml injectable; Ativan 2 mg/ml, 4 mg/ml injectable; Versed (midazolam) 1 mg/ml, 5 mg/ml injectable.

Typical adult dose: clonazepam or lorazepam, test dose of 0.5 mg hs, then 0.5 mg bid. Load in emergency: Diazepam and lorazepam can be given intravenously and midazolam i.v. or i.m. for emergencies - see texts and package insert for details. Increase to target for clonazepam or lorazepam of 1.5 - 3 mg/d divided into 3 doses; diazepam 6-15 mg/d.
divided into 3 doses; clorazepate 7.5 – 60 mg per day in 2 or 3 doses.

Typical pediatric dose of clonazepam: 3.75 – 20 mg/d in 2 or 3 divided doses.

Metabolism: various routes via liver and kidney.

Half-life: clonazepam – 24 to 48 hours; clorazepate - active metabolite about 48 hours; diazepam – 24 to 48 hours.

Therapeutic plasma concentrations: diazepam 150-700 nanograms/ml; clonazepam 20-80 nanograms/ml.

Pregnancy: Category D – believed able to cause birth defects in humans.

Clonazepam (Klonopin) will be used as an example of BDZ drug interactions.

Drugs that raise CLN levels: nafazodone,

Drugs that lower CLN levels: rifampin

CLN increases sedative effects of: antihistamines, antipsychotics, antifungals, phenobarbital, other BDZs, opiates, trazodone, tricyclics.

CLN decreases effects of other drugs: none listed

Dangerous side effects: respiratory depression or arrest, impairment of consciousness, low blood pressure (hypotension), blood or liver injury, birth defects.

Common side effects: Sedation, cognitive impairment, light-headedness, dizziness.

Other side effects: behavior and personality changes, attention deficit and hyperactivity, GI upset (rare), constipation, sexual dysfunction, rash or itching, headaches.

**Carbamazepine (Tegretol, Novartis; Carbatrol)**

Carbamazepine has been in use in Europe since the 1950's and the United States since the 1960's. No drug has been shown to be more effective for partial seizures. Advantages of carbamazepine include its effectiveness in partial and secondarily generalized seizures, and probably primarily generalized seizures. It is not effective for absence, atonic or myoclonic seizures. Carbamazepine is less sedating than are the barbiturates, and it probably is equivalent to phenytoin in this regard. Carbamazepine does not produce cosmetic side effects. Blood levels of carbamazepine easily are measured and an increase in dose produces a smooth increase in blood levels.

The typical carbamazepine dose in adults is 600 – 1,600 mg orally divided into 3 or 4 doses. These doses can safely be exceeded for intractable epilepsy patients. Therapeutic serum levels range 4 - 12 mg/L. Carbamazepine is metabolized to the 10, 11-epoxide, which may contribute to hidden toxicity to the medication.

Disadvantages of carbamazepine include the need to dose on a three or four times daily basis. This problem is partially obviated by the Tegretol-XR or the Carbatrol dosing forms, each of which can be taken twice daily. Carbamazepine can cause GI upset and double vision. It can lead to reversible decreases in white count, distinct from aplastic anemia, but still in need of following. Serum sodium declines in about 5% of people on chronic carbamazepine, sometimes limiting its use. Rare cases of liver toxicity necessitate monitoring of blood tests. At least as many people are allergic to carbamazepine as to phenytoin: in one European study over 10% of people started on carbamazepine monotherapy developed a rash. Carbamazepine tablets inactivate easily in hot, moist environments (e.g., bathrooms) or in the sun. This problem can occur with all seizure medications, but particularly with carbamazepine.

If you use the Tegretol-XR form, you should know that empty pills are excreted in the stool – this is normal. Neither Tegretol-XR nor Carbatrol should be cut into pieces, since the intact capsule confers the slow release.

**Summary data for carbamazepine**

**Pill sizes:**

| Tegretol | 100 mg (round, speckled white, chewable) |
| Tegretol-XR | 100 mg (round orange pill with a T) |
| | 200 mg (round orange pill with a T) |
| Carbatrol | 200 mg (turquoise/black & “200”) |
| | 300 mg (turquoise/black & “300”) |

**Liquid for oral:** suspension 100 mg/5 ml.

Injectable: None available.

Typical adult dose: Start with 100 mg twice a day. Increase 100 mg every 3-7 days to 400 – 1600 mg per day. It is not practical to load CBZ in an emergency.
Typical pediatric dose: 10-35 mg/kg/d, divided into 2-4 doses.

Metabolism: Liver (CYP 3A4). Becomes the epoxide. Excreted in urine.

Half-life: around 12 hours after a few weeks of use. Therapeutic plasma concentrations: 4-12 mcg/ml.

Pregnancy: Category D - known to cause birth defects in humans.

Drugs that raise CBZ levels: Grapefruit juice (not a drug, but can seriously raise CBZ levels), antifungals, cimetidine, diltiazem, erythromycins (very significant), fluoxetine, isoniazid, omeprazole, protease inhibitors, propoxyphene (highly significant), verapamil. Felbamate and valproate increase the epoxide metabolite.

Drugs that lower CBZ levels: felbamate (but increases epoxide metabolite), methsuximide, phenobarbital, phenytoin.

CBZ increases effects of: acetaminophen toxicity, benzodiazepines, clozapine bone marrow toxicity, lithium, MAO inhibitors (serious toxic interaction).

CBZ decreases effects of other drugs: acetaminophen efficacy, antipsychotics, antifungals, buproprion, buspirone, coumadin, cyclosporin, felbamate, lamotrigine, methadone, narcotics, neuromuscular blockers, oral contraceptives, protease inhibitors, quetiapine, quinidine, risperidone, theophylline, thyroid hormone, tiagabine, topiramate, tricyclics, valproate, zonisamide.

Dangerous side effects: Blood toxicity, liver toxicity, Stevens-Johnson skin rash, severe lowering of serum sodium, birth defects, worsening of certain seizure types (atypical absence).

Common side effects: blurred vision, GI upset

Other side effects: mild weight gain, unsteadiness, dizziness, mild lowering of blood counts, mild water retention and lowering of serum sodium, rash, mouth sores, sensitivity to the sun, behavior and personality changes, sexual dysfunction, inactivation of birth control pills.

Ethosuximide

Ethosuximide is a drug of choice for pure absence (petit mal) seizures. It is not effective against generalized tonic-clonic (grand mal) seizures. Ethosuximide has been around since the early 1950’s. If absence seizures are intermixed with convulsions, then a broad-spectrum antiepileptic drug such as Depakote, Lamictal, Topamax, or Zoneregran is required. Alternatively, two drugs can be used, such as Zarontin plus Dilantin or Tegetrol.

Ethosuximide has a half-life of several days in the blood, which would allow single daily dosing. However, GI sensitivity often requires splitting the dose.

Summary data for ethosuximide

Pill sizes: 250 mg capsules (red, shiny).

Liquid for oral: 250 mg/5 ml suspension.

Injectable: none.

Typical adult dose: 500 mg per day in 2 divided doses, increase over a few weeks to 500-1500 mg/d in 2 or 3 divided doses. Half-life would permit daily dosing, but GI side effects might require splitting the dose.

Typical pediatric dose: Start with 10 mg/kg/d in 2 or 3 divided doses. Increase over weeks to 15-40 mg/kg/d.

Metabolism: Mainly liver, 3A4 system.

Half-life: 30-40 hr in kids, 50-60 in adults

Serum levels: 40-100 mcg/ml

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that raise ESM levels: valproic acid

ESM decreases effects of other drugs: Lamotrigine, estrogen (may make birth control pills less effective),

Dangerous side effects: rare serious behavior problems or psychosis, rare blood counts

Common side effects: GI upset, sleepiness.

Other side effects: dizziness, headaches, rash.

Felbamate (Felbatol)

Felbamate, released in 1994, was the first new antiepileptic medication in the United States in 15 years. Hopes were initially high, based upon clinical trials that showed good safety and efficacy. Clinical trials are performed on two to five thousand individuals, and low-incidence side effects may not become evident until the
medication is in the field. As the drug approached 100,000 patient years of exposure, it became clear that complications were occurring. Thirty-one cases of aplastic anemia (serious injury to the blood and bone marrow) were reported, along with several cases of liver failure. A few of these complications were fatal. The drug was almost withdrawn from the market, but the FDA decided to let it stay with stern labeling, since it was the only effective drug for some individuals with epilepsy.

Prior to the concern about aplastic anemia, it was evident that felbamate had a unique profile of common side effects, including GI upset, weight loss, insomnia, and tendency to induce behavior problems, particularly in mentally impaired children and adults. Some individuals who are troubled by weight gain and sleepiness find felbamate particularly useful.

Felbamate indications were broad spectrum for a variety of seizure types. It has efficacy against atonic seizures, as well as partial and secondarily generalized seizures. Felbamate has substantial drug interactions, which make it difficult to use in conjunction with other medications. A typical adult dose of felbamate is 400-1200 mg orally three times per day (total of 1200 - 3600 mg per day). Frequent monitoring of blood counts and liver tests are necessary if felbamate is to be used. It should only be used when all other reasonable alternatives have been tried and found inadequate.

Summary data for felbamate

Pill sizes: 400 , 600 (scored) mg tan capsules.

Liquid for oral: suspension 600 mg/5ml.

Injectable: none

Typical adult dose: 900 mg divided as ½ of a 600 mg tablet three times per day. Increase 300 mg daily every 3-7 days to a target dose of 1,800 mg divided into 3 doses. Dosing can go as high as 3,600 mg per day.

Typical pediatric dose: 15 mg/kg/d in 3 divided doses, increase as tolerated up to 45 mg/kg/d.

Metabolism: 50% by various liver systems and 50% kidney and other routes.

Half-life: 12-18 hours.

Serum levels: not established.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that raise FLB levels: Valproate

Drugs that lower FLB levels: phenytoin, carbamazepine (but raises epoxide metabolite levels), phenobarbital.

FLB increases effects of: phenobarbital, phenytoin, valproate, carbamazepine epoxide.

FLB decreases effects of other drugs: oral contraceptives.

Dangerous side effects: aplastic anemia, liver failure. The risk of a serious, and potentially fatal, complication is estimated at 1-in-2000.

Common side effects: GI upset, headache, insomnia, weight loss.

Other side effects: behavior and personality changes (especially in children), sexual dysfunction, rash or itching, blurred vision, unsteadiness, dizziness, anxiety, depression, altered taste.

Gabapentin (Neurontin)

Gabapentin was the second new antiepileptic medication released in the wave of new medicines in the mid 1990’s. Gabapentin is useful for treatment of partial and secondarily generalized seizures. It is not effective for absence, atonic seizures or myoclonic seizures. Gabapentin also has an indication for neuropathic pain.

Advantages of gabapentin include its lack of drug interactions. It does not change levels of other seizure medications. It is cleared by the kidney, so it does not interact at the level of the liver. Gabapentin is normally very well-tolerated, occasionally producing dizziness, unsteadiness, sleepiness and uncommonly GI side effects, as well as rare other side effects. Patients may feel better on gabapentin than they do on other older antiepileptic medications. This may be particularly useful for the elderly, who are quite drug sensitive, and individuals who are on the verge of not wanting to be treated at all.

Disadvantages of gabapentin include the short half-life which requires a three times daily regimen. Gabapentin has a reputation for being less effective than other medications against partial seizures, although it clearly is effective. This reputation comes from a typical responder rate (the fraction of patients whose seizures are cut in half or better) in the range of 20-30%. In fairness to gabapentin, these studies were done at low doses of the medicine, in the range of 900-1800 mg, and as add-on therapy in cases of very hard-to-treat seizures. There is an unproven, but
plausible belief that efficacy is better at doses up to 3600 or even 4800 mg of gabapentin per day. Serum levels are not very useful. Gabapentin often is used as an add-on medication to another seizure medicine.

Summary data for gabapentin

Pill sizes:
  Capsules
    100 mg (white)
    300 mg (yellow)
    400 mg (orange)
  Tablets
    600 mg (oval, tan, not scored)
    800 mg (oval, white, not scored)

Liquid for oral: suspension 250 mg/5ml.

Injectable: none

Typical adult dose: 300 mg day one, 600 m day two, 900 mg day 3 divided into 3 doses. Can also start 900 mg divided into 3 doses. Maintenance is 900 – 4800 mg/d divided into 3 or 4 doses.

Typical pediatric dose: start with 10-15 mg/kg/d in 3 divided doses, increase as tolerated up to 60 mg/kg/d.

Metabolism: excreted unchanged in the kidney.

Half-life: 12-18 hours.

Serum levels: 2-20 mcg/L, not very useful.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that raise GPN levels: none

Drugs that lower GPN levels: antacids (minor effect)

GPN increases effects of: carbamazepine (increased dizziness through unknown action)

GPN decreases effects of other drugs: none known. GPN does not affect oral contraceptives.

Dangerous side effects: very rare reduction of blood counts, possible birth defects.

Common side effects: dizziness, unsteadiness, fatigue.

Other side effects: cognitive problems, weight gain, GI problems, slurred speech, fluid retention and edema, muscle aches, mood changes.

Lacosamide (Vimpat)

Vimpat (VIM-pat) is the brand name used in the United States and some other countries for the seizure medicine lacosamide (la-COS-a-mide). In the United States, the Food and Drug Administration (FDA) approved lacosamide in 2008 to be used seizure medicine in adults with partial-onset epilepsy.

Brain cells need to work (fire) at a certain rate to function normally. During a seizure, brain cells are forced to work much more rapidly than normal. How Vimpat helps prevent brain cells from working as fast as a seizure requires is still being investigated. One mechanism appears to be an effect on the sodium channels in the brain that control firing rates of nerve cells. Two other commonly-used seizure medications, phenytoin (Dilantin) and carbamazepine (Tegretol) affect nerve cell sodium channels, but in a different way. Vimpat acts on a slower-acting component of the sodium channel. Vimpat also works on a protein in nerve cells called collapsin response mediator protein-2 (CRMP-2). This protein controls growth of nerve cell processes, such as axons. Action on CRMP-2 so far seems to be unique among seizure medications, but how it might help to control seizures is unknown.

Summary data for lacosamide

Pill sizes:
  50 mg (pink)
  100 mg (dark yellow)
  150 mg (salmon)
  200 mg (blue) film-coated tablets

Liquid for Oral: None

Injectable
  200 mg/20 mL single-use vial for intravenous use

Typical adult dose: Usually, your doctor will tell you to start by taking 50 mg twice daily (100 mg/day). The dose may be increased at weekly intervals by 100 mg/day given as two divided doses to a daily dose of 200 to 400 mg/day, based on how well it works and how well you tolerate it.

Typical pediatric dose: not established.

Metabolism: After taking Vimpat tablets, peak blood levels are reached in 1-4 hours. The half-life of Vimpat (the amount of time it takes for the blood level to fall by 50%) is generally around 13 hours. Vimpat is usually taken two times a day. Vimpat is partially metabolized in the liver by the enzyme system called CYP2C19, and it is then cleared from the body in the urine, via the kidneys. People with poor kidney func-
tion usually need to take less Vimpat and may take it less often, because it stays in their body longer.

Serum levels: not established.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs interactions: Minimal. Does not affect oral contraceptives.

Dangerous side effects: rare effects on cardiac (heart) conduction, with prolongation of the PR or QT intervals. Blood tests sometimes show abnormalities in patients taking Vimpat. Liver abnormalities were seen in blood tests of 7 of 935 patients (0.7%). A few patients had lowering of blood counts which could potentially lead to anemia or lowering of resistance to infection.

Common side effects: Dizziness, imbalance, headache, nausea, vomiting, diarrhea, double vision, vision blurred, sleepiness, fatigue, tremor, memory loss.

Other side effects: behavior change, anxiety, rare decrease of red blood cells, liver injury, heart rhythm problems.

**Lamotrigine (Lamictal)**

Lamotrigine was the third drug (after felbamate and gabapentin) in the wave of new antiepileptic medications introduced in the mid-1990’s. In the United States, the drug has an indication for partial and secondarily generalized seizures. Nevertheless, lamotrigine is a true broad-spectrum anti-seizure medication and may have its most dramatic successes in treatment of generalized seizures. The use of the medication has been limited by an approximately 5-15% incidence of rash. This is an unusual type of rash, dependent upon the rate lamotrigine is started: with more rash at faster initiation rates. If the patient is already on valproic acid, then the risk of rash is further increased. Rash typically begins as itchy or blotchy red regions on the face, arms or trunk. The rash usually improves within three days of stopping lamotrigine (or sometimes even with reduction of dose), and resolves in 1-2 weeks. Rash on mucous membranes such as mouth, eyes or genital regions, or any blistering of skin, suggests a potentially more serious type of rash. The serious rash, called Stevens-Johnson syndrome or toxic epidermal necrosis, may require hospitalization, and rarely has been fatal. The slow titration mandated by the risk of rash makes it difficult to achieve therapeutic doses of lamotrigine in less than a month.

In clinical trials of lamotrigine, responder rates were similar to those of gabapentin, in the 20-30% range for add-on therapy in patients with uncontrolled seizures. As with gabapentin, few intractable patients became seizure free when lamotrigine was used as add-on therapy. Clinical experience has demonstrated higher responder rates in less severely affected patients, and in patients with generalized seizures. Advantages of lamotrigine include its broad spectrum, its very good tolerance profile (with occasional problems of dizziness, ataxia, sleepiness, or GI upset, as well as a variety of other less common side effects, and the rash). Clinical studies were performed in the 300-500 mg per day range, but field use has gone to 800 mg, or even higher. Lamotrigine has the advantage of single daily dosing, but patients also taking phenytoin, carbamazepine, phenobarbital, topiramate, zonisamide, tiagabine, felbamate, or other inducers of liver metabolism, need to take lamotrigine twice a day. Serious adverse events other than rash are quite rare.

Be aware of the sound-alike drug, Lamisil, an over-the-counter anti-fungal medicine, sometimes mistakenly substituted for Lamictal!

**Summary data for lamotrigine**

Pill sizes: 2, 5, 25 mg chewable-dispersible tablets

- Tablets, 6-sided “shields”
  - 25 mg (white)
  - 100 mg (orange)
  - 150 mg (peach-tan)
  - 200 mg (blue)

Liquid for oral: none.

Injectable: none.

Typical adult dose: In patients not on valproate, the manufacturer recommends starting with 50 mg/d divided into two dose for 2 weeks, then 100 mg/d divided into two doses for 2 weeks, then increase by 100 mg daily every two weeks. I find it simpler and better tolerated to start with 25 mg per day for a week, and then increase each week by 25 mg daily (1 pill) on a twice a day schedule until at 100 mg (4 pills) twice a day. I then switch to 100 mg pills, and increase to 100 mg in the am and 200 mg in the pm for a week, then 200 mg in the am and pm (400 mg/d). In patients on valproate, I cut the above dosages in half and aim for 150-250 mg/d in 1 or 2 doses.

Typical pediatric dose: If not on valproate start 0.6 mg/kg/d, increase over 1-2 months to 5-15 mg/kg/d in 1-2 divided doses. If on valproate, start at 0.15 mg/kg/d and increase over 2-3 months to 1-5 mg/kg/d.

Metabolism: liver, the N-glucuronidation pathway.
Half-life: about 24 hours in monotherapy; 12 hours in conjunction with Dilantin, Tegretol, phenobarbital, Trileptal; 72 hours with valproate

Serum levels: 2-20 mcg/L, not very useful.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that raise LTG levels: VPA, sertraline.

Drugs that lower LTG levels: Dilantin, phenobarbital, Mysoline, Tegretol, Trileptal, Zarontin

LTG usually does not raise or lower levels of other AEDs (thought the reverse does occur).

LTG decreases effects of other drugs: VPA. Does not affect oral contraceptives.

Dangerous side effects: serious rash (Stevens-Johnson syndrome, toxic epidermal necrolysis); rare liver injury; production of myoclonic seizures with toxic doses.

Common side effects: rash in 5-10%, especially early in use; dizziness, GI upset, somnolence.

Other side effects: usually few, if no rash; may occasionally get headache or blurred vision.

**Levetiracetam (Keppra)**

Levetiracetam (Keppra) was introduced in 2000. It is chemically based upon a drug called piracetam, which is used in Europe to improve cognition. Piracetam and levetiracetam probably do not improve cognition to any significant extent, but at least levetiracetam appears to have minimal deleterious effects on thinking. Levetiracetam is approved as an add-on medicine for partial seizures, including partial seizures with secondary generalization. Experience is suggesting that it may have broad-spectrum action against all seizure types. The initial dose of 1,000 mg daily (500 mg twice a day), may be a therapeutic dosage for some. This allows rapid titration to efficacy. Levetiracetam is not metabolized in the liver and it has very few drug interactions. In most cases, the drug appears to be quite effective with a low incidence of significant side effects.

**Summary data for levetiracetam**

Pill sizes:
- 250 mg (blue tab, scored)
- 500 mg (yellow tab, scored)
- 750 mg (orange tab, scored)

Liquid for oral: none.

Injectable: none.

Typical adult dose: Manufacturer recommends 1,000 mg divided into two doses. This may be an effective dose right from the start. In individuals who are sensitive to medicine side effects, I split the capsules and begin with 500 mg per day in two divided doses. Typical adult maintenance dose is 1,000 – 3,000 mg/d in two divided doses.

Typical pediatric dose: not established.

Metabolism: mainly processed in the kidney, does not involve the liver.

Half-life: 6-8 hours, longer with kidney dysfunction.

Serum levels: unknown.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that raise LVT levels: None known.

Drugs that lower LVT levels: None known.

LVT increases effects of: None known.

LVT decreases effects of other drugs: None known. Does not affect oral contraceptives.

Dangerous side effects: Rare psychiatric side effects, such as hallucinations, delusions, that resolve within 1-2 weeks after stopping drugs. Since Keppra is a new drug, other rare serious side effects might emerge.

Common side effects: Usually few or no side effects, but can have sleepiness, fatigue, dizziness, unsteadiness, headache.

Other side effects: behavior change, anxiety, rare decrease of red blood cells.

**Methsuximide (Celontin)**

Methsuximide (Celontin) is an old antiepileptic drug, typically used as a third-string agent when other drugs have failed. It is chemically related to ethosuximide (Zarontin), but has a different profile of action. Celontin is a broad-spectrum drug, with actions against partial seizures and absence (petit mal) seizures.
Summary data for methsuximide

Pill sizes: 150, 300 mg (yellow) capsules.

Liquid for oral: none.

Injectable: none.

Typical adult dose: Initial 150-300 mg/d, increased over a few weeks to a target dose of 300 – 1,200 mg/d in 1-2 divided doses.

Typical pediatric dose: Start with 150 mg/d, increased over a few weeks to a target of 150-1,200 mg/d in 1-2 divided doses.

Metabolism: liver metabolism via the CYP 2C9 system to the active metabolite, N-desmethylmethsuximide (NDM).

Half-life: The NDM metabolite has a half-life of 24-72 hours.

Serum levels: 10-40 mcg/ml of the NDM metabolite.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that raise MSM levels: Dilantin, phenobarbital, Felbatol.

Drugs that lower MSM levels: Tegretol (but increases the epoxide metabolite)

MSM increases effects of: Dilantin, phenobarbital, carbamazepine epoxide

MSM decreases effects of other drugs:

Dangerous side effects: rare blood count problems.

Common side effects: GI upset, dizziness, sleepiness, headache

Other side effects: Behavior changes, irritability, skin rash, hiccups.

Oxcarbazepine (Trileptal)

Oxcarbazepine (Trileptal) is not yet well known in the US medical community, but is a drug of some importance in the treatment of partial and secondarily generalized seizures. The FDA has approved use of Trileptal as a first-line drug in monotherapy (as a single drug). Oxcarbazepine is structurally identical to carbamazepine (Tegretol), except for a double-bond oxygen molecule (a keto group) on the 10-11 position of the triple-ring structure. This oxygen molecule prevents metabolism to the epoxide form of the drug. Since the epoxide form accounts for some of the toxicity of Tegretol, Trileptal may have a better therapeutic/toxic profile, at least in some users. Trileptal is not effective against absence or myoclonic seizures.

Trileptal is a different drug from Tegretol / Tegretol-XR / Carbatrol, although in the same family. Advantages of Trileptal over the older carbamazepines include: fewer drug interactions, need to take only twice daily, less autoinduction in the liver (the phenomenon of lower blood levels on constant dose because of increased liver clearance in the first 2 months of use), less interference with oral contraceptives; possibly better therapeutic ratio. The side effects of oxcarbazepine are similar to those of carbamazepine.

A side effect seen more with Trileptal than Tegretol is hyponatremia, or low blood sodium. The blood sodium is low, not from a deficiency of salt, but because of greater retention of water, which dilutes the sodium. Normal serum sodium is 135-145 mEq/L. At serum sodium concentrations less than 120 mEq/L, people can become confused and experience worsening of seizures. Effects tend to be more severe in cases of rapid reduction of sodium, compared to declines over many weeks. Excessively rapid correction of low sodium also can cause problems. I usually reduce or discontinue Trileptal or Tegretol for serum sodium less than 125 mEq/L, but each case should be considered in the context of how much the drug is helping the seizures, and whether there are good alternatives.

No drug, old or new, has been proven to be more effective than is carbamazepine (Tegretol) for partial seizures. Given that oxcarbazepine has similar effectiveness to that of carbamazepine, and may have fewer side effects (except for hyponatremia), it stands out as a first-line drug for many patients. I sometimes use it as a first drug of choice for partial seizures, with or without secondary generalization. The reasons against using it in all patients (versus the more traditional Tegretol or Dilantin) are higher cost and less of a long-term track record.

Summary data for oxcarbazepine

Pill sizes: 150, 300 600 mg all tan, scored tablets.

Liquid for oral: 300 mg/5 ml suspension.

Injectable: None, although the active metabolite, monohydroxy derivative has been in clinical trials for intravenous use.
Typical adult dose: The manufacturer recommends a starting dose of 600 mg per day. My experience is that this results in excessive toxicity. If seizures are not very severe or frequent, I begin with 300 mg/d (150 mg twice a day), and increase 150 mg per week to a target daily dose of 1,200 – 2,400 mg/d. If a patient is on Tegretol, then I immediately switch to approximately the same daily milligrams of Trileptal, and over the next few weeks, increase to 1.5 times the daily milligrams of Tegretol.

Typical pediatric dose: Start with 8-10 mg/kg/d (maximum 600 mg/d), and increase over several weeks to 20-50 mg/kg/d.

Metabolism: Metabolized outside the liver to the monohydroxy derivative (MHD), which is the active compound. The MHD then is eliminated by glucuronidation in the liver.

Half-life: The active MHD metabolite has a half-life of 8-10 hrs, longer in patients with kidney disease.

Serum levels: MHD metabolite 12-30 mcg/ml.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that raise OXC levels:

Drugs that lower OXC levels: Dilantin, phenobarbital, carbamazepine.

OXC increases effects of: Dilantin, tricyclic antidepressants.

OXC decreases effects of other drugs: Lamotrigine, felodipine, dihydropyridine calcium blockers, Verapamil, oral contraceptives.

Dangerous side effects: Worsening of seizures (especially atypical absence) with toxic doses.

Common side effects: blurred vision, sedation, dizziness, unsteadiness, GI upset.

Other side effects: behavior or mood changes, headaches, rash, inactivation of birth control pills.

Phenobarbital (Luminal)

Phenobarbital was invented in 1912, and is perhaps the most used medicine worldwide because it can be given in a single daily dose and it costs less than $5.00 per hundred pills. Nevertheless, it is a sedating medication and produces a significant incidence of depression and cognitive problems. Epilepsy specialists usually consider it a second-line drug.

Phenobarbital has the advantage of being cheap, used with a single daily dose, safe, not requiring a lot of blood tests for checks of blood counts and liver function, and available in both oral and injectable forms. The injectable form can be given i.v. or i.m. Disadvantages are several. First, the drug is sedative. It often impairs thinking and memory. Depression can be significant with barbiturates and an appreciable risk for suicide can emerge, particularly in a population that already is prone to depression. The half-life of phenobarbital is long, meaning that the medicine takes a long time to get into and out of the system. Without a loading dose the medication takes up to two weeks to come to steady state levels, and lingers a long time when the pills are stopped. A typical dose of phenobarbital is 100 mg per day. The dose does not need to be split, although by long-standing and unnecessary practice it often is divided into 30 mg three times a day.

Summary data for phenobarbital

Pill sizes: 15, 16.2, 30, 32, 60, 65, 97, 100 mg – all little white pills (DO NOT mix up sizes!)

Liquid for oral: 15, 20, 30, 60, 65, 130 mg/5 ml.

Injectable: 30 mg/ml, 60 mg/ml, 130 mg/ml. The injection can be given i.v., but it is irritating intramuscularly.

Typical adult dose: Start with 30-100 mg per day. Increase over a week to 60-200 mg/d (1-3.5 mg/kg). Because of the long half-life of phenobarbital, levels will build up slowly over weeks. To load in an emergency: 10-20 mg/kg intravenously.

Typical pediatric dose: 3-7 mg/kg/d.

Metabolism: metabolized by the liver (CYP 2C9), excreted in the urine.

Half-life: 2-5 days.

Plasma concentrations: 15-40 mcg/ml.

Pregnancy: Category D - known to cause birth defects in humans.

Drugs that raise PBB levels: valproate, felbamate.

Drugs that lower PBB levels: phenytoin (sometimes)
PBB increases effects of: acetaminophen, antidepressants, antipsychotics, antihistamines, benzodiazepines, opiates.

Decreases effects of other drugs: bupropion, buspirone, corticosteroids, Coumadin (interaction lowers INR, increases clotting), cyclosporine, doxycyclin, lamotrigine, oral contraceptives, oxcarbazepine, phenytin, protease inhibitors, quinidine, theophylline, thyroid hormone, topiramate, zonisamide.

Dangerous side effects: severe depression, suicide, Stevens-Johnson rash, blood count suppression, liver injury, worsening of porphyria, addiction, birth defects; rare worsening of seizures with toxic doses.

Commonest side effects: sleepiness, fatigue, cognitive impairment, depression, hyperactivity in children and elderly.

Other side effects: sedation, depression, cognitive impairment, attention deficit, hyperactivity, behavior and personality changes, dizziness, sexual dysfunction, rash or itching, sensitivity to the sun, anemia, nausea, vomiting, connective tissue growth (frozen shoulder, hand contractions), bone weakening, neuropathy-numbness, inactivates birth control pills.

Phenytoin (Dilantin)

Phenytoin was introduced in 1938 as the first non-sedating antiepileptic medication. It is the most popular drug in the United States for treatment of partial and secondarily generalized seizures. A typical phenytoin dose is 100 mg orally, three times a day, but with brand name Dilantin the half-life is 24 hours and the medication can usually be tolerated in a single daily 300 mg dose. The therapeutic serum level of phenytoin is 10-20 mg/L.

Advantages of phenytoin include long experience, single daily dose regimen for good compliance, no need for a taper-up schedule, relatively quick disappearance of the medication after stopping. Disadvantages include mild to moderate sedation and cognitive effects. The medication can have unpleasant cosmetic side effects, such as thickening of skin, acne, undesired hair growth, and gum swelling. Some of these cosmetic side effects may not be reversible after stopping medication. A moderate number of people are allergic to phenytoin, and one in ten thousand suffer the serious Stevens-Johnson allergic skin reaction, which can be fatal. Phenytoin can cause a deficiency of folate (folic acid, a vitamin) and vitamin D, occasionally leading to anemia and bone problems. Phenytoin can also produce a peripheral neuropathy, which may be felt as numbness and tingling or weakness in the feet and fingers. People who are on phenytoin for years may benefit from a daily multivita-

min, since the B complex may counteract neuropathy, the D the bony changes, and the folic acid a tendency of phenytoin to reduce that vitamin.

Small increases in phenytoin dose sometimes produce skyrocketing levels with toxicity. Note that the 100 mg and 30 mg brand-name pill are long-acting, but the 50 mg chewable Infa-tab is short-acting. Note that generic phenytoin may show variable absorption and half-life. In an acute situation where i.v. administration is needed, the fosphenytoin (Cerebyx) form is less irritating to veins, and tissues, and may be less likely than is phenytoin to produce cardiac arrhythmias. It is, however, more expensive.

Summary data for phenytoin

Pill sizes:
- 30 mg (white capsule / pink stripe, long-acting)
- 50 mg (triangular chewable tab, short-acting)
- 100 mg (white capsule / orange stripe, long-acting)

Injectable: 50 mg/ml injectable i.v. only (not a Pfizer product). Preferable to give fosphenytoin 20 mg phenytoin equivalent/kg load at <150 mg/min.

Typical adult dose: 300 mg per day (no titration only), with a target maintenance of 200-500/day in 1-3 divided doses. Load in emergency: i.v. load 20 mg per kg, max 50 mg/min. Oral load 20 mg/kg in 3 divided doses over a day.

Typical pediatric dose: 5-10 mg/kg/d, divided into two.

Metabolism: Liver (CYP 2C9).

Half-life: around 24 hours.

Therapeutic plasma concentrations: 10-20 mcg/ml.
Therapeutic unbound (free) concentrations: 1-2 mcg/ml.

Pregnancy: Category D - known to cause birth defects in humans.

Drugs that raise PHT levels: amiodarone, cimetidine, diliazem, erythromycins, fluconazole, fluoxetine, isoniazid, methsuximide, methylphenidate, metronidazole, modafenil, omeprazole, oxcarbazepine, phenobarbital (sometimes), ritonavir, sertraline, ticlopidine, topiramate, trimethaprim, valproate.

Drugs that lower PHT levels: antacids, carbamazepine, ciprofloxin, doxyrubicin, phenobarbital (sometimes), primidone, rifampin, sucralfate
PHT increases effects of: Coumadin (interaction sometimes raises INR, decreases clotting), acetaminophen

PHT decreases effects of other drugs: antipsychotics, antifungals, bupropion, buspirone, carbamazepine, clozapine, corticosteroids, Coumadin (interaction usually lowers INR, increases clotting), cyclosporin, felbamate, lamotrigine, mifepristone, narcotics, neuromuscular blockers, oral contraceptives, protease inhibitors, quetiapine, quinidine, thyroid hormone, tiagabine, theophylline, topiramate, tricyclics, valproate, zonisamide

Dangerous side effects: Blood toxicity, liver toxicity, Stevens-Johnson skin rash, lupus-like syndrome, worsening of certain seizure types (atypical absence), birth defects; rare worsening of seizures with toxic doses.

Common side effects: unsteadiness, mild fatigue, mild cognitive slowing.

Other side effects: Dizziness, unsteadiness, cosmetic problems increased face/body hair and coarser skin), gum overgrowth, acne, skin rash, sensitivity to the sun, swollen lymph nodes (rare), anemia (rare), nausea (uncommon), tremor (uncommon), slurred speech, blurred vision, confusion, sleepiness, behavior and personality changes, fever, headache, inactivation of birth control pills, sexual dysfunction, neuropathy (tingling/numbness), weakening of the bones from vitamin D block.

**Pregabalin (Lyrica)**

Pregabalin is chemically similar to gabapentin (Neurontin), and also has shown efficacy for seizures and neuropathic pain. In clinical trials, a median reduction of partial seizures was seen in 37% of subjects taking 300 mg per day, and 51% reduction with 600 mg. The responder rate (% with at least a 50% reduction in seizure frequency) was about 50% for patients on doses of 600 mg per day. For intractable seizures, this is a good responder rate in add-on trials. It is indicated for partial onset seizures, with or without secondary generalization.

**Summary data for pregabalin**

Pill sizes: 25, 50, 75, 100, 150, 200, 225, 300

Liquid for oral: None.

Injectable: None.

Typical adult dose: 150 – 600 mg/day divided into two or three doses. Dose should be reduced for patients with renal failure.

Metabolism: Negligible metabolism, most of the drug is excreted unchanged in the urine. It does not undergo hepatic metabolism.

Half-life: 6-7 hours.

Pregnancy: Category C, can cause birth defects in test animals, not known to cause birth defects in people.

Drugs that raise PGB levels: none known.

Drugs that lower PGB levels: none known.

PGB increases effects of: none known, except a few studies have shown mild increase of phenytoin levels.

PGB decreases effects of other drugs: none known.

Dangerous side effects: rare anaphylaxis, rare serious skin reaction, worsening of heart failure, rare muscle-joint pains, rare severe reduction of blood counts.

Commonest side effects: dizziness, sleepiness, unsteadiness, weight gain, tremor

Other side effects: double or blurry vision, cognitive or memory impairment, headaches, dry mouth.

**Primidone (Mysoline)**

Primidone (Mysoline) is an older antiepileptic medication with similarity to phenobarbital. Primidone is itself an active antiepileptic drug. It is metabolized to phenobarbital (long-lasting) and PEMA (phenyl-ethyl-malonic acid, short-acting), two additional antiepileptic drugs. Mysoline is useful for partial seizures with or without secondary generalization. It may be better than is phenobarbital for myoclonic seizures, such as juvenile myoclonic epilepsy. In another arena, primidone is used to reduce hand and head tremor.

In the VA Cooperative Study of Antiepileptic Drugs, primidone exceeded the ability of phenytoin, carbamazepine and phenobarbital to control secondarily generalized tonic-clonic (grand mal) seizures, provided that the patient did not discontinue Mysoline because of sleepiness.

The limiting factor in primidone use is sedation. Primidone also has all of the side effects of phenobarbital, because it is metabolized to phenobarbital. Most patients should try a single test-dose of primidone 50 mg to see if they have an excessive degree of sedation. If they do not, then they can progress to the 250 mg pills.
Discontinuation of primidone can be very difficult. Primidone is a habit-forming drug, with withdrawal symptoms of seizures, anxiety, insomnia, and tremor. Unless side effects mandate rapid withdrawal, tapering should be very slow, over an interval of many months, using the 50 mg pills to decrease slowly.

Summary data for primidone

Pill sizes:
- 50 mg (square tab, grey, scored)
- 250 mg (square tab, yellow, scored)

Liquid for oral: None.

Injectable: None, but can substitute phenobarbital if unable to take primidone. The conversion is 10-to-1: 250 mg of primidone for 25 mg of phenobarbital.

Typical adult dose: 50 mg test dose to check for excessive sleepiness. If OK, then 125 mg at night for 3-7 days, then increase by 125 mg every 3-7 days to target dose of 750 – 2,000 mg/d in divided doses of 3-4 times per day.

Typical pediatric dose: 10-25 mg/kg/d in 3 divided doses.

Metabolism: half excreted unchanged in the kidney and half metabolized in the liver to PEMA and phenobarbital.

Half-life: primidone 8-24 hr; PEMA 10-24 hr; phenobarbital metabolite 2-5 days.

Serum levels: primidone 5-12 mcg/ml; phenobarbital 15-40 mcg/ml.

Pregnancy: Category D – can cause birth defects in humans.

Drugs that raise PRM levels: Valproate, Felbamate, INH.

Drugs that lower PRM levels: phenobarbital, Dilantin, Tegretol.

PRM increases effects of: acetaminophen, antidepressants, antipsychotics, antihistamines, benzodiazepines, opiates.

PRM decreases effects of other drugs: bupropion, buspirone, corticosteroids, Coumadin (interaction lowers INR, increases clotting), cyclosporine, doxycycline, lamotrigine, oral contraceptives, oxcarbazepine, phenytoin, protease inhibitors, quinidine, theophylline, thyroid hormone, topiramate, zonisamide; inactivates oral contraceptives.

Dangerous side effects (similar to phenobarbital, but more sedation): severe depression, suicide, Stevens-Johnson rash, blood count suppression, liver injury, worsening of porphyria, addiction, birth defects; rare worsening of seizures with toxic doses.

Commonest side effects: sleepiness, fatigue, cognitive impairment, depression, hyperactivity in children and elderly.

Other side effects: sedation, depression, cognitive impairment, attention deficit, hyperactivity, behavior and personality changes, dizziness, sexual dysfunction, rash or itching, sensitivity to the sun, anemia, nausea, vomiting, connective tissue growth (frozen shoulder, hand contractions), bone weakening, neuropathy-numbness, inactivates birth control pills.

Rufinamide (Banzel)

Banzel (BAN-zel) is the brand name used in the United States and some other countries for the seizure medicine rufinamide (ru-FIN-a-mide). In the United States, the Food and Drug Administration (FDA) approved rufinamide in 2008 to be used as an add-on (adjunctive) seizure medicine in children 4 years and older and adults with the Lennox-Gastaut (LGS) syndrome. The LGS is an epilepsy syndrome that usually is difficult to treat. It can comprise multiple seizure types, including atonic (drop), tonic (stiffening), tonic-clonic (stiffening and jerking), absence (staring) and other seizure types. Cognitive impairment or intellectual delay can accompany the syndrome.

Brain cells (neurons) need to work (fire) at a certain rate to function normally. During a seizure, brain cells are forced to work much more rapidly than normal. How Banzel helps prevent brain cells from working as fast as a seizure requires is still being investigated, but it may slow down rapidly firing neurons. One mechanism appears to be an effect on the sodium channels in the brain that control firing rates of nerve cells. Two other commonly-used seizure medications, phenytoin (Dilantin) and carbamazepine (Tegretol) also affect nerve cell sodium channels.

Summary data for rufinamide

Pill sizes:
- 200 mg pink, oblong, scored
- 400 mg pink, oblong, scored

Liquid for oral: none.

Injectable: none.

Typical adult starting dose: For adults, the manufacturer recommends a starting dose of 200 mg twice a day, but you and
your doctor may choose to start more slowly or more rapidly to fit your particular needs. Dosing can be increased by adding an extra 200 (or 400) mg twice a day every two days, to a maximum of 1600 mg twice a day (3200 mg per day total).

Typical pediatric dose: Children will usually be started at doses of approximately 10 mg/kg/day administered in two equally divided doses. Dosing can increase by adding additional 10 mg/kg amounts every two days, until the child is taking 45 mg/kg/day or a maximum of 3200 mg/day, divided into two doses each day.

Metabolism: After taking Banzel tablets, peak blood levels are reached in 4-6 hours, so absorption is slow compared to many other drugs. Absorption may be faster when Banzel is taken with food. The half-life of Banzel (the amount of time it takes for the blood level to fall by 50%) is generally around 8 hours. Banzel is usually taken two times a day, which will produce some peaks and valleys in the blood levels of the drug. Banzel is extensively metabolized (but not by the usual liver cytochrome CYP system) then cleared from the body in the urine, via the kidneys. Despite being cleared by the kidneys, people with kidney disease were found to have about the same blood levels of rufinamide as people with normal kidney function.

Serum levels: not established, but doses of 45 mg/kg/d produced serum levels of 5-50 micrograms/ml.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drug interactions: Can increase phenytoin levels. Rufinamide levels can be decreased by several other antiepileptic drugs.

Common side effects: Headache, dizziness, unsteadiness, fatigue, sleepiness, nausea, vomiting, abdominal pain, constipation, tremor, blurred vision, anxiety.

Tiagabine (Gabitril)

Tiagabine is a “designer drug,” formulated to block inactivation (uptake) of the brain’s main inhibitory neurotransmitter, GABA. When more GABA accumulates in the brain, seizures are harder to initiate and sustain. Gabitril is useful for partial and secondarily generalized seizures. It is not effective for absence or myoclonic seizures. The side effect profile is acceptable, with some sedation, abnormal thinking, and dizziness. Scattered reports have detailed paradoxical worsening of seizures from tiagabine, and a few serious psychiatric complications. Tiagabine has a short half-life, but has been documented to be effective on a twice-daily basis.

Summary data for tiagabine

Pill sizes:
- 2 mg tablet
- 4 mg (yellow tablet, not scored)
- 12 mg (green tablet, not scored)
- 16 mg (blue tablet, not scored)
- 20 mg (pink tablet, not scored)

Liquid for oral: none.

Injectable: none.

Typical adult dose: Begin with 4 mg at bedtime for a week, then increase 4 mg each week to 16-56 mg/d in two divided doses.

Typical pediatric dose: 4-32 mg/d in 2-4 divided doses.

Metabolism: liver metabolism by the CYP 3A4 system.

Half-life: 4-10 hours.

Serum levels: not established.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that lower TGB levels: Dilantin, phenobarbital, Tegretol.

Dangerous side effects: rare induction of nonconvulsive status epilepticus (prolonged confusional seizures); rare psychosis or hallucinations.

Common side effects: sleepiness, dizziness, imbalance, thinking difficulty, stomach upset.

Other side effects: personality change, tremor,

Topiramate (Topamax)

Topiramate was just released in 1997. It is a sulfonated drug, like acetazolamide (Diamox) and tizanamide. As such, it produces occasional allergic reactions, and may precipitate kidney stones. Topiramate is a substantially effective medication, with responder rates in the 50% range in intractable epilepsy. It also has the advantage of being a broad-spectrum antiepileptic medication, in a
category with valproic acid, lamotrigine, zonisamide, and benzodiazepines. Topiramate is given in a twice-daily dosing regimen, typically in doses of 200-400 mg total per day. However, this typical dose may in fact be too high, and evidence is accumulating that doses in the 100-200 mg per day range may be effective without as many side effects. The usual side effects include dizziness, sleepiness and unsteadiness. In addition, the medication produces temporary impairment of thinking and memory in about 30% of full doses. Subtle impairments, such as slow thinking and slow talking, noticed mainly by family may occur in even more. Cognitive problems are more common in people taking doses of topiramate higher than 400 mg per day, during initiation of the drug, and in people on topiramate in combination with other AEDs (polypharmacy).

I use topiramate when I want a powerful, broad-spectrum AED, but its use is limited by a relatively high incidence of thinking problems, a risk for kidney stones, glaucoma and the need to start the drug slowly. Because of kidney stone risk, topiramate theoretically probably should not be used in conjunction with zonisamide (Zonegran) or acetazolamide (Diamox), although no actual proof exists for high kidney stone risk with such combination therapy. Some people like the common weight loss side effect of topiramate; others find it to be a problem.

Summary data for topiramate

Pill sizes: 15, 25 mg sprinkle capsule;
   25 mg (round white tablet, not scored)
   100 mg (round peach tablet, not scored)
   200 mg (round salmon tablet, not scored)

Liquid for oral: none.

Injectable: none.

Typical adult starting dose: 25-50 mg in 1-2 divided doses.

Typical adult dose: 400-600 mg per day in 2 divided doses. Some do better on as little as 100-200 mg/d. I usually start with 25 mg per week, and increase by 25 mg daily each week to 200 mg in a twice-daily dose. I then switch to 100 mg pills and move to 100, 200 mg per day for a week, then 200, 200 mg (400 mg/d) as a target dose.

Typical pediatric dose: Start 1-3 mg/kg/d, then increase over a month or two to 5-9 mg/kg/d.

Metabolism: 70% unchanged in the kidney when the only drug, but more complex with polypharmacy.

Half-life: 12-30 hours, longer with kidney failure.

Serum levels: not established

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that lower TPM levels: Dilantin, Tegretol, phenobarbital

TPM increases effects of: Dilantin, Diamox (more kidney stone risk), Zonegran (more kidney stone risk),

TPM decreases effects of other drugs: Oral contraceptives.

Dangerous side effects: Severe thinking impairment, kidney stones (2-3%), behavior problems, precipitation of acute glaucoma.

Common side effects: Thinking impairment, GI upset, dizziness, sleepiness, unsteadiness, weight loss.

Other side effects: Dizziness, numbness.

Valproic Acid (Depakote, Depakene, Depacon)

Valproic acid is particularly useful for the primary generalized epilepsies, including true grand mal, absence not responsive to ethosuximide, and atonic seizures. It also has some action in partial and secondarily generalized seizures. This makes it a “broad spectrum” antiepileptic medication.

Advantages of valproic acid are efficacy for generalized seizures and the broad spectrum, which sometimes covers more than one seizure type with one medication. Disadvantages include significant GI upset in many patients, the need to ease people into the drug slowly to avoid side effects, and a relatively high incidence of liver problems, which requires monitoring of liver tests in the blood. Liver problems are particularly a danger in children under five years of age on multiple medications. Typical doses for adults are in the range of 250-1000 mg three times a day (750 - 3000 mg per day). Depakote-ER can be used for a twice-daily extended release pill, and Depacon for intravenous use in emergencies.

Summary data for valproic acid

Pill sizes:
   Depakene 250 mg (orange capsule)
   Depakote 125 mg (blue-white sprinkle capsule)
   Depakote 125 mg (dark orange tab, not scored)
   Depakote 250 mg (peach tab, not scored)
   Depakote 500 mg (pink tab, not scored)
   Depakote-ER 500 mg extended-release tab.
Liquid for oral: 250 mg/5ml syrup.

Injectable: Depacon 100 mg/ml.

Typical adult starting dose: 125 mg three time a day. Increase every 3-7 days by 125 mg daily.

Load in emergency: Depacon 10-15 mg/kg or a dose equivalent to the oral dose. Load over 1 hour.

Typical adult dose: 750 – 4000 mg/d
Typical pediatric dose: 15-60 mg/kg/d divided in 2-4 doses.

Metabolism: Liver metabolism by the glucuronidation system.

Half-life: 8-15 hours.

Therapeutic plasma concentrations: 50 – 125 mcg/ml.

Pregnancy: Category D - known to cause birth defects in humans.

Drugs that raise VPA levels: aspirin (also can increase bleeding risk), cimetidine, erythromycins, felbamate, fluoxetine, isoniazid.

Drugs that lower VPA levels: carbamazepine, cholestyramine, lamotrigine, phenobarbital, phenytoin, rifampin, ritonavir.

VPA increases effects of: carbamazepine (increased epoxide), coumadin, ethosuximide, felbamate, lamotrigine, nonsteroidal anti-inflammatory drugs such as ibuprofen, naproxyn, etc. (increased bleeding risk), phenobarbital, phenytoin (increases free levels), primidone, zidovudine.

VPA decreases effects of other drugs: clozapine.

Dangerous side effects: liver toxicity, blood toxicity, pancreatitis, birth defects (especially open spine)

Common side effects: GI upset, tremor, significant weight gain, thinning or loss of hair.

Other side effects: rash, weight loss, water retention and lowered sodium, increased bleeding/bruising, sensitivity to the sun, blurred vision, headaches, joint aches and pains, behavior and personality changes, menstrual irregularities, sexual dysfunction, elevation of blood ammonia levels.

Vigabatrin is marketed in most major countries around the world, excluding the United States and Japan, where regulatory approval has not been forthcoming, because of effects of the drug on vision and the retina. Vigabatrin is another “designer drug,” that works by blocking metabolism of GABA, the brain’s main inhibitory neurotransmitter. Accumulation of GABA inhibits seizures. Sabril is effective for partial and secondarily generalized seizures, but it also has efficacy in certain pediatric syndromes, such as infantile spasms, which are very difficult to treat with other medications. Vigabatrin has apparently good efficacy as an add-on drug for intractable partial seizures, with half of people having seizures reduced by at least 50%.

Typical side effects of vigabatrin include dizziness, unsteadiness, sleepiness, and mild thinking or memory impairment, but thinking is usually clearer than with many of the older medications. A few percent of treated patients develop depression or other serious psychiatric problems, which reverses when the medication is discontinued. The U.S. FDA has denied release of vigabatrin because of visual field changes, in up to 30% of people who take vigabatrin for more than a year. These visual field changes may or may not be noticed by the patient, as loss of peripheral vision, but specialize ophthalmological testing can disclose the inability to see in patches outside the central regions of one or both eyes. Rarely, the visual loss involves central fields of vision, which can cause problems with reading and gross seeing. Visual field changes result from a toxic effect of vigabatrin on the retina. Visual field changes can be permanent, even after stopping vigabatrin. Therefore, use of the drug requires demonstration that no alternatives are effective for the seizures. Regular checking of visual fields by historical queries, clinical exams, and eye tests are important.

Summary data for vigabatrin

Pill sizes: 500 mg

Liquid for oral: none.

Injectable: none.

Typical adult dose: the manufacturer recommends 1,000 mg/d divided into two doses. I prefer to start with 500 mg at night for a week, then twice a day for a week, then 500 mg in the am and 1,000 mg in the pm for a week, then 1,000 mg twice a day for a week. Target dose is 1,000 – 3,000 mg per day divided into two daily doses. Half-life would permit daily dosing, but GI side effects might require splitting the dose.

Vigabatrin (Sabril)
Typical pediatric dose: I start with 250 mg per day, and increase over several weeks to 500 – 2,000 mg/d.

Metabolism: VGB irreversibly inhibits GABA-transaminase, the key enzyme for breaking down GABA. Vigabatrin is mainly cleared by the kidney.

Half-life: The relevant effect is inhibition of GABA-transaminase, which lasts about 5 days.

Serum levels: not relevant.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

VGB decreases effects of other drugs: Can lower efficacy of Dilantin, by an unknown mechanism.

Dangerous side effects: Retinal toxicity, with visual loss; rare psychiatric side effects including psychosis and hallucinations; rare induction of myoclonic or nonconvulsive seizures with toxic doses. Vigabatrin causes loss of nerve linings (myelin) in animal models, a condition allied to multiple sclerosis, but no such action has been found in humans.

Common side effects: sleepiness, dizziness, GI upset, blurred vision.

Other side effects: headache, personality changes, rash (rare).

**Zonisamide (Zonegran)**

Zonisamide (Zonegran) is a sulfonamide-related drug, similar in many ways to topiramate. Zonegran is a broad-spectrum antiepileptic drug, useful for partial, secondarily generalized, absence, and myoclonic seizure types. Zonisamide may control myoclonic seizures in cases for which all other drugs have failed.

Early clinical trials with zonisamide in the US were halted because of a high incidence of kidney stones. Trials continued in Japan and elsewhere, whereby the kidney stone risk was determined to be 2-4%. US trials were resumed and the drug was shown to be relatively safe and effective. Because of the theoretical additive risk for kidney stones, zonisamide should not be used in conjunction with topiramate (Topamax), acetazolamide (Diamox), or other drugs know to provoke stones.

Zonisamide, like topiramate, can cause cognitive (thinking) problems in a significant minority of those taking the drug, but the incidence of cognitive problems probably is a little lower than with topiramate (at least in the approved dosages). Weight loss is common, viewed favorably by some patients; unfavorably by others.

**Summary data for zonisamide**

Pill sizes: 100 mg red-white capsule.

Liquid for oral: none.

Injectable: none.

Typical adult dose: start with 100 mg at night for 2 weeks, then increase by 100 mg daily every 2 weeks to a target dose of 200 – 600 mg/d in 1 or 2 daily doses. Half-life would permit daily dosing, but GI side effects might require splitting the dose.

Typical pediatric dose: Pediatric dosing is difficult because of the limited dosage forms. In older children, can start with 2-4 mg/kg/d and increase over weeks to a few months to a target of 4-8 mg/kg/d.

Metabolism: one-third excreted unchanged in the kidney, two-thirds metabolized in the liver by the CYP 3A4 system and acetylation.

Half-life: In monotherapy 2-3 days. With enzyme inducers (Dilantin, Tegretol, phenobarbital, etc.) 1-2 days.

Serum levels: 10 – 30 mcg/ml.

Pregnancy: Category C – can cause birth defects in animals, unknown in humans.

Drugs that lower ZNS levels: Dilantin, phenobarbital, primidone, Tegretol.

ZNS decreases effects of other drugs: Since it is metabolized by the CYP 3A system, it could theoretically inactivate oral contraceptives.

Dangerous side effects: Kidney stones in 2-4%; birth control pill failure; rare blood count or liver problems; serious rash (Stevens-Johnson syndrome or toxic epidermal necrolysis), rare heat stroke.

Common side effects: cognitive (thinking) problems, sleepiness, dizziness, unsteadiness, double vision, GI upset, weight loss.

Other side effects: ordinary skin rash, personality change, depression, headaches, insomnia.
Other Medications

A long and growing list of other antiepileptic medications are under various stages of development. It is not likely that all of these drugs will survive in the marketplace, competing for the same group of patients with intractable partial and secondarily generalized seizures. Any new drug will have to have an obvious benefit in terms of efficacy, safety, tolerance, novel mechanism, ease-of-use, or cost.

Explaining Prescriptions

The prescription, traditionally abbreviated as “Rx,” is the means by which the doctor communicates with the pharmacy. Prescriptions can be written on pre-printed pads or plain pieces of paper; it is the instructions and doctor’s signature that make it legal, not the printing. Prescriptions can be communicated over the phone to the pharmacy with no writing at all. However, certain highly controlled drugs, such as narcotics, may require written prescriptions. A medical license to prescribe drugs is given by the State, so a prescription might not be honored across State lines. In practice, most pharmacists do accept intra-State prescriptions for non-controlled medications.

A prescription specifies the name of the drug, the number of milligrams in each pill or liquid, the number of doses and amounts to be given each time of day, the number of pills to be dispensed, and the number of automatic refills allowed. The prescription also specifies whether brand name drugs or cheaper generic drugs should be used (see discussion below). Abbreviations on a prescription, based upon ancient Latin terminology, commonly include the following:

qd = once a day
bid = twice a day
tid = three times a day
qid = four times a day
qod = every other day
qam = every morning
qpm = every evening
qh = every hour of sleep (at bedtime)
qac = before each meal
qpc = after each meal
prn = as needed
po = by mouth
pr = rectally
sl = sublingually
iv = intravenously
im = intramuscularly
sc = subcutaneously
in = intranasally
gtt = drops

Numbers are written with vertical bars and redundant dots above the bars, for example, two vertical lines with a horizontal bar and two dots over it means “2.”

Patients often request large supplies of seizure medicines, or extra medicines to take on trips, for emergencies, etc. The medical team is sympathetic to such requests, but it usually is up to the insurance company paying for the pills. Most of the time, third-party payers will allow only one-month supply at a time. Sometimes patients can purchase bulk quantities of medicines. This makes sense once a regimen is well established. This can be renewed. Physicians typically give between 2-11 monthly automatic renewals, depending upon frequency of visits and how stable the patient is on a particular medication.

Most seizure medicines are expensive, the exceptions being the old-timers, such as phenobarbital and Dilantin. The newer seizure medicines can cost $300 per month. If a patient is on multiple medications, then cost accumulates to very high levels. The reason for these high prices is that invention of a new medication costs the drug companies hundreds of millions of dollars. Most new medicines never make it to market. The companies charge enough on those that do to make their money back (and some profit as well). Insurance companies may or may not pay for prescription medicines. Sometimes they pay a certain amount minus a co-pay of $5-35 dollars per prescription. The insurers all have formularies that list their preferred medications. Medicines in the formulary are better covered by insurance than are medicines not in the formulary. Sometimes physicians can get individual permission to use a medicine for a particular patient, but this requires time and paperwork. Doctors usually do not know what insurance plans cover which medicines, because there are so many plans.

If your doctor has prescribed a medicine that is not on your plan, and therefore is beyond your ability to afford, ask your insurance representative what seizure medicines are covered. Then contact your doctor’s office to see if any of these are reasonable alternatives. DO NOT take the approach of dropping the issue, since this could leave you without any medication. Ordinary Medicare does not cover prescription drugs at all, a large political issue. Some of the HMO Medicare plans trade other benefits or increased cost for some prescription coverage. Medicaid (Medical in California) covers most of the seizure medicines, but needs a form called a “Treatment Authorization Request” (TAR) for approval of use of the newer medications. Your doctors office may have some free samples, but only enough to get you started. Drug companies sometimes have compassio-
nate use programs, with free medicines for patients who cannot afford them. Ask your doctor about these programs.

Generic medications are less expensive alternatives to brand name medicines. Generics become available when the brand-name patent expires. The advantage of generic medicines is the lower cost. The disadvantage is the uncertainty that it has been manufactured as well as has the original brand name medicine. The value of generics is controversial. My belief is that generics usually are reliable, but generic seizure medicines are not as reliable as are the brand name medications. The main problem is how much medicine gets absorbed into your system. The FDA requires that bioavailability (the amount available to be absorbed into your body) of a generic drug be plus-or-minus 20% of the bioavailability of the brand name drug. Since pharmacies may stock different generic drugs each week, this could lead to a 40% fluctuation in serum levels of antiepileptic drugs, potentially enough to cause seizures or medication side effects. If your seizures are infrequent and your payment plan mandates much higher cost for brand drugs, then generics are the best alternative. If you have uncontrolled seizures, then brand name seizure drugs are more reliable. Doctors can specify on a prescription that the brand name drug is required. However, the pharmacy then has the right to charge the patient the difference in cost between what the insurance company will pay and the cost of the brand drug. If the doctor does not specify "brand name," in most states the pharmacist can substitute a generic drug.

Switching medicines

It is one thing to describe the pros and cons of individual medications. It is another to switch from one medicine to another. Even if a seizure medication is not working as desired, removing it can produce withdrawal seizures. Adding any new medicine, no matter how safe in general, introduces an unknown, which could produce unexpected side effects. Therefore, the patient should perceive a clear reason to change medications. Usually these reasons include inadequate seizure control, excessive side effects, or both. Emergence of a new drug on the marketplace is not, in itself, a good reason to initiate a change.

Most switches of seizure medicines require a period of overlap. The new drug usually cannot be added in full protective dose until a build-up schedule allows a person’s system to become used to the drug. Sudden discontinuation of an old drug can lead to withdrawal seizures. A switch of seizure medication therefore comprises a few potentially unpleasant weeks, during which a person is on more medication, and subject to withdrawal symptoms. A few exceptions exist for which sudden changes are reasonable, for example, Trileptal in place of Tegretol. If a medication is causing an allergy or other severe side effects, then sudden discontinuation may be the only good alternative. Changes of medicine regimens are complicated. The patient and family should have a written schedule detailing changes day-by-day or week-by-week. Typical change regimens decrease the old pills and increase the new pills every 3, 7, 14, or 30 days. The rate of switch will be individualized according to the severity of seizures, side effects and the properties of the drugs being changed. Phone access to the treating physician or nurse is very useful during seizure medication changes, since reaction of the individual to a new medication is not entirely predictable.

Research Testing of New Drugs

At some point in the development of every promising new drug for epilepsy, it must be tried in people with seizures. If asked to volunteer for a trial of a new drug, you should seriously consider doing so. You will be helping the community of people with epilepsy, and you may help yourself by getting a good new drug that is not available by any other means.

Drug trials are not like regular therapy, because the medical team is obliged to give medication according to a protocol. The protocol is developed before opening the trial to patients, by the sponsoring company and regulatory bodies. The protocol specifies all details of treatment with the experimental drug: who is eligible to get it, what other medications are allowed during the testing, what dose or doses of drug should be used, how fast it should be started, under what conditions it should be stopped, what tests are done, how long the drug can be used, how and when doctor visits must take place, and so on. The patient and the physician always have the right to quit a trial at any point, but they do not have the right to alter the rules of the protocol. In effect, license is granted to use the drug only under very specific conditions. This is different from use of a regular prescription drug, where the doctor and patient can tailor, adjust, or change the drug regimen to obtain the best effect in an individual patient.

Many, but not all, drug trials require the use of a placebo. A placebo, sometimes called a “sugar pill”, is an inactive pill made to look like the study drug. Some patients in the trial receive the real drug and some receive the placebo. Neither the patient nor the medical team know who is getting a placebo, although the information is made available by the drug company in case of an emergency that requires knowledge of treatment. The placebo is required by FDA rules of testing to eliminate drugs that really do not work, but just make people think that they work because of excessive optimism, desire to please, or more attention paid to people during a trial. Most trials have provisions to provide the active drug to all participants at some point (usual-
ly after a test phase), since it is unfair to volunteer without ever having a chance to try the drug.

The main concern in all drug trials is safety of the study participants. If there is a conflict between following a protocol and keeping an individual patient safe or well, then the safety issue must be addressed first. All protocols are reviewed by an objective body, called an “Institutional Review Board” or IRB, that verifies that the drug appears to be safe, the protocol is well-designed, and all possible safeguards are in place in case of unexpected problems.

Every drug has side effects, and new drugs can have unexpected side effects. Each participant will be asked to read and sign a document of “informed consent” which lists the reasons for doing the testing, what you can expect to happen during the testing, what are the possible benefits, what are the risks, and what to do if you have problems. No one should ever be forced to participate in drug trials. Just because you are eligible, does not mean that you need to participate. You should be offered alternative treatments, or when none exist, no treatment at all. If the trial seems right for you, however, it may provide a useful treatment to you years earlier than you would otherwise be able to get it.

**Stopping Seizure Medicines**

Are antiepileptic drugs forever?

Your doctor has prescribed antiepileptic drugs (AEDs). Perhaps you are holding a first-time prescription, or perhaps you have been taking them for 30 years. Either way, once you are on AEDs, is there an exit strategy? Or are AEDs forever?

As with so many aspects of epilepsy care, the answers depend upon individual circumstances. Some people are given AEDs to cover them over a few months of an acute illness that provoked a seizure, and then the treatment may comprise only a few months. At the other extreme is therapy for a potentially life-long hereditary condition, such as juvenile myoclonic epilepsy, which tends not to disappear. Most treatment plans fall in the middle, not brief, but also not forever.

Obviously, there are both pros and cons to stopping therapy. On the pro side is reduction in side effects or the possibility of future side effects from the AEDs. Not all side effects are immediately evident. Chronic loss of bone density, predisposing to osteoporosis and fractures, occurs silently over decades, particularly with the older AEDs such as Dilantin (phenytoin), Tegretol (carbamazepine) and Depakote (valproic acid). Some people, who do not notice that their thinking and memory is impaired by sedative medicines, such as phenobarbital, feel much sharper once they are off the medicine. Many seizure medicines interact with other drugs, making general medical care more complex. AEDs can be expensive. And important for some is the bother of having to remember to take the pills, to pack them, and to renew them every month. Even the idea of needing medicine and the associated stigma is philosophically distasteful to some people.

Arrayed against this long list of potential benefits of stopping AEDs is one big “con” – the increased risk of having a seizure. From such a seizure, you may incur injury, or even in the worse case SUDEP, the rare tragedy of sudden unexplained death in epilepsy. You may embarrass yourself, or put your job at risk. And a seizure may precipitate suspension of your driving license. If fact, many doctors, including me, advise not to drive when tapering that last AED, for at least three months from the start of the taper. Perhaps for these reasons, the majority of the seizure-free adults studied in the British Medical Research Council Drug Withdrawal study (Chadwick et al. 1996) chose to remain on AEDs. The risk to lifestyle of children caused by withdrawing AEDs may be less than that to adults, because of the lack of driving and employment issues in children.

Should a seizure be prevented at all cost, because one seizure renders the next more likely? As claimed over a century ago by Sir William Gowers: “...the tendency of the disease [epilepsy] is toward self-perpetuation; each attack facilitates the occurrence of the next by increasing the instability of the nerve elements.” (Gowers 1881). The modern view, although still somewhat controversial, is that treatment of the seizure does not influence the long-term prognosis (Sander 1993; Shinnar and Berg 1996). Therefore, there is probably little long-term risk of an attempted AED withdrawal leading to worsening seizure disorder. However, it may be a struggle to regain seizure control once it is lost, and it may take some time to do so.

How often does withdrawal succeed? Relapse rates among various published studies range from 12 – 63% (Britton 2002), with the most definitive study being the Medical Research Council study of over a 1013 patients (MRC Study Group, British Medical Journal 1993): 22% of patients who continued antiepileptic drug treatment had a recurrence of seizures within two years compared to 41% who slowly
stopped treatment. A study of 531 patients with epilepsy (Lamdhade and Taori 2002) showed these factors to be associated with seizures coming back: seizure onset late in life, seizures for more than three years, more than 30 total seizures, a positive family history of epilepsy, focal neurological deficits such as partial numbness or paralysis, epilepsy-associated findings on the electroencephalogram (EEG), and underlying ongoing structural or genetic causes for having seizures. Not predictive of whether tapering AEDs would succeed were gender, seizure frequency, and number of AED drugs used. A study (Specchio et al. 2002) compared outcome for 225 patients who chose to discontinue AEDs, compared to 105 patients who chose to continue therapy. All had been seizure-free for at least two years. Overall, 50% of the patients who stopped medications had a seizure, versus 28% who remained on treatment. Calculated relative risk was 2.9-fold greater for patients coming completely off medicines. The probability of being seizure-free was 88% at 6 months, 82% at 24 months, 80% at 36 months, and 68% at 60 months.

As a rule of thumb, if you have been seizure-free for 2-5 years, have none of the negative risk factors mentioned above, and you go off your AEDs, you have about a two-thirds chance of remaining seizure-free for another five years. Conversely, 1-in-3 will have a seizure with medication discontinuation. Be aware of small seizures, the simple partial, complex partial or absence (petit mal) episodes. You should be free of these as well before tapering medications, not just the big, obvious seizures.

When do seizures return after AED withdrawal? One study (Berg and Shinnar 1994) of relapse rate showed that, among patients seizure-free on AEDs for 2-4 years, 75% remained seizure-free at one year and 71% at two years after discontinuing the medications. In this analysis, 60-80% of the recurrences occurred within one year. In a study from Turkey (Aktekin 2006), the probability of having a seizure after tapering AEDs was 29% at 1 month, 14% at 3 months, 4% at 6 months, 7% at 12 months, 18% at 24 months, and 7% at 36 months. Most of the risk of having a seizure is within the first two years of stopping medicines, and most of that risk is probably within the first few months. Unfortunately, there is no time when you can conclude you are “home free.” Seizures can come back many years after withdrawing AEDs. The longer you go without a seizure, the smaller the chances that they will return.

How quickly should medications be tapered? Anecdotal experience from patient-initiated discontinuations, and from experiences in epilepsy monitoring units (Yen et al. 2001), suggest that severe seizures or even status epilepticus can result from immediate discontinuation of therapeutic doses of medications. Tennison and coworkers (1994) randomized children being withdrawn from AEDs to a 6-week or 9-month course of taper, after at least two-years of freedom from seizures. The groups did not differ in relapse rates, thereby favoring the easier 6-week course. However, patients on barbiturates and benzodiazepines were not adequately studied in this series, and additional caution is warranted for these drugs. Do not stop your seizure medications suddenly unless there is an emergency need to stop. It could be dangerous to stop suddenly! Work with your doctor to design a tapering schedule.

One randomized, controlled study from Norway (Lossius and colleagues, 2008) emphasized the trade-off. People whose AEDs were tapered after being seizure-free for two years improved their neuropsychological test scores compared with those who stayed on medicines. But those who tapered AEDs had a 2.5-fold increased risk of having a seizure.

In conclusion, antiepileptic medication taper can be worthwhile after at least 2-5 years of freedom from seizures. Patients should not have an ongoing brain abnormality or genetic predisposition for seizures, should not have had major prior problems withdrawing from medications, and should not have epilepsy-like activity on a recent EEG. If an adult, they must be willing to refrain from driving for at least three months from the start of the taper (some argue for longer), and must be willing to accept about a one-third risk of relapsing with a seizure. If, on the other hand, the patient worries about seizures more than about medications, then continuation of AEDs likely will minimize the risk for future seizures. This is another area in which the clinician can be an educator, and the patient a decision-maker. Ultimately, it is your choice.

Uncontrolled (Refractory) Epilepsy

Seizures come under control with medicines in about 2 of 3 people with epilepsy. Seizures that do not come under control are called “intractable,” or “refractory.” The definition of control is variable. For many, one seizure a year is far too many; others are not bothered by one a week. In a general sense, seizures are refractory if they are frequent and severe enough or the required therapy for them troublesome enough, to seriously interfere with quality of life. Seizures can be uncontrolled for three broad reasons: 1. The diagnosis is wrong; 2. The treatment is wrong; 3. The seizures do not respond to the best diagnosis and treatment.

An incorrect diagnosis of epilepsy is more common than most people might think. One chart review study by Smith and colleagues in England concluded that 13% of patients referred for refractory epilepsy did not have epilepsy. If seizures are not controlled, then a reasonable first question is: “Are the episodes really seizures?” A large number of conditions can imitate seizures, as discussed in the epilepsy.com video.
A second reason for uncontrolled seizures is suboptimal treatment. Some medicines are not right for some types of seizures. Carbamazepine (Tegretol), for example is usually good for treating complex partial seizures, but not absence seizures. Ethosuximide (Zarontin) is good for absence, but not complex partial seizures. Since absence and complex partial seizures can occasionally be confused with each other, there is a chance for using an ineffective medicine. Medications can be used in the wrong dose: too low to protect against seizures, or too high as to cause severe side effects. The newer seizure medicines often have fewer side effects than do the older seizure medicines. Information about the seizure medicines can be found on epilepsy.com.

Polypharmacy is the employment of several medications at once to treat the same condition. Some people require more than one drug to control their epilepsy, but additional AEDs rarely lead to complete freedom from seizures. Patients taking polypharmacy may have so many side effects that it is difficult to increase dosage for any of their AEDs to an effective level. Furthermore, polypharmacy can lead to drug interactions that limit effectiveness or increase side effects of another drug. Therefore, one good treatment for refractory seizures in people taking polypharmacy is a streamlining of medicines.

Missing medication is a cause of breakthrough seizures. Refer to epilepsy.com for more information on compliance and strategies for remembering to take epilepsy medicine. It can make a real difference!

Complicating factors, such as illness, sleep deprivation or extreme stress, can make seizures more difficult to control. These again vary with the individual. Individual precipitating factors include alcohol, exercise, flashing lights or certain visual patterns, general illness, heavy breathing (hyperventilation), taking certain medications, the menstrual cycle, missing medications, missing sleep, recreational drugs, and stress. All too often, a seizure breakthrough is preceded by one of these, or other personally relevant, factors.

True intractable epilepsy can result from seizures that are “too strong” to be controlled by medication, or by intolerance of medication. Seizures that might be easy to treat with medicine become hard to treat when the most effective medicines result in allergy or intolerable side effects. Multiple drug resistance is a condition in which people are resistant to multiple medications. Some people with multiple drug resistance have a type of metabolism that quickly inactivates or isolates drugs, causing them to be less effective. Another common experience in treating refractory epilepsy is “honey-mooning,” or as it is officially known, developing medication tolerance. In this situation, a new drug works for a few months and then becomes ineffective. The cycle repeats with each new medication.

When confronted with refractory seizures, various courses of action become available to physicians and to patients. The doctor can reevaluate the diagnosis and the medication therapy. The person with epilepsy can consider strategies for remembering to take medications and reduction of precipitating factors, if any. People whose seizures are not under control should be referred to an Epilepsy Center. You can look up epilepsy physician specialists and epilepsy centers near you at epilepsy.com. An Epilepsy Center takes a comprehensive approach to medical, psychological and social problems associated with seizures.

When medications do not work, then non-medication therapy for the epilepsy can be considered. Epilepsy surgery is a reasonable option for people with refractory epilepsy, provided that the seizure origin in the brain can be localized to one region, and that region is safe to remove. Success rates for cessation or near-cessation of seizures ranges from about 50-90%, depending upon the cause of seizures and their brain location. Serious complications occur with about 1 in every 50 surgeries. Epilepsy surgery is elective surgery, meaning that it is a matter of personal choice, not necessity. Considerable information is available on epilepsy.com about epilepsy surgery, but this is an issue to be discussed with your medical care team.

Vagus nerve stimulation (VNS) is another option for refractory seizures. It rarely stops seizures entirely, but it provides significant help in about half of the people who try it. A stimulator is implanted under the skin of the chest and connected to the left vagus nerve in the neck. Side effects of VNS are usually mild, including hoarseness and coughing, mostly while becoming use to the stimulation. VNS also is approved by the FDA for depression that does not respond to other treatments.

The ketogenic diet is a high fat, high protein and very low carbohydrate diet, similar to the Atkins Diet used for weight loss. If is used mainly for children with uncontrolled seizures, but it has also been useful for some adults. The KD alters the chemistry of the brain in an as yet poorly understood way, but the result is fewer seizures. See the Ketogenic Diet section of epilepsy.com.

Experimental trials. If other alternatives are not attractive, then participation in an experimental trial of new medications, device or surgical procedures may be a good option. New therapies are developed by clinical trials. Supervision and safety controls are extensive, but there still is an element of risk and the unknown. If a trial is successful, you may receive a useful new therapy years before it becomes available to the public.
Intractable epilepsy does not always remain intractable. First, one of the treatments listed above may prove effective. Second, individuals may be able to modify precipitating factors or their lifestyle to help to control the seizures. But even in the absence of specific therapies or life changes, there is hope for improvement. Jacqueline French and associates studied 246 patients from their clinic with at least one seizure per month and inadequate relief from at least two antiepileptic drugs. Over a three-year follow-up period, 5% of these patients each year became seizure-free for at least six months. Unfavorable predictors of control were chronic cognitive impairment, long history of intractable seizures and previous status epilepticus.

Refractory (uncontrolled) epilepsy is a heavy burden. A physician needs to make certain that the diagnosis of epilepsy is correct and that the proper medicines are being used in the best way for that person. The individual with epilepsy needs to look at things they can do to better control their seizures, such as remembering medicines, staying generally healthy, getting good sleep, minimizing stress and avoiding seizure-precipitating conditions. Non-drug therapies, such as epilepsy surgery, vagus nerve stimulation or experimental clinical trials, may be good options for some patients. But even when all seems hopeless for control, 5% of people (1 out of 20) with refractory epilepsy get better each year. There are always grounds for hope. The biggest hope is for new therapies to prevent and cure epilepsy.

EPILEPSY SURGERY

Anti-epileptic drug therapy is effective in approximately two-thirds of people with epilepsy, implying that one-in-three do not obtain good seizure control or have unacceptable side effects from medications. The concept of good seizure control is elusive. How long must a person go without a seizure before control is considered good? This is a matter of individual opinion. In some states, an individual cannot obtain a driver’s license if he or she has had a seizure within one year. Good control might therefore represent being seizure-free for one year. The standard is often set too low, with physicians who believe that a seizure or two every month or even every few months is not “too bad.” But such a seizure frequency can have a major impact on the quality of life of people with epilepsy. Conceptually, seizures are not in good control if their occurrence, at any numerical frequency, restricts the quality of life. Part of the challenge of epilepsy specialists is to encourage treating physicians and patients to strive for better control of seizures, and not to be complacent about the limitations imposed by occasional seizures.

Candidates for Epilepsy Surgery

Some people who cannot be controlled with medications are candidates for surgery to cure their epilepsy. Counts of potentially eligible candidates range in the 20,000 - 100,000 range in the United States. Since only a few thousand operations are done each year, it is apparent that surgery for epilepsy is under-utilized. This is an issue of education, availability of epilepsy treatment resources and expense. Epilepsy surgery is costly, with the evaluation process, surgery, and recovery phase typically costing more than $50,000 in the United States. However, economic analyses taking into account the direct and indirect medical costs of uncontrolled seizures indicate that the money can be recovered over several years. Most insurance agencies, including Medicare, State Medical Assistance programs and private carriers, pay for epilepsy surgery in qualified candidates.

Good candidates for epilepsy surgery meet the following criteria:
- The diagnosis of epilepsy is secure
- Seizures are not adequately controlled after trying at least two antiepileptic drugs
- The onset site for seizures (the “seizure focus”) can be localized to one place in brain
- The seizure focus is in an area of brain that is safe to remove
- General health and social support systems (family, etc.) will allow surgery and recovery
- The person or caregiver understands the likely benefits and risks and desires surgery

Pre-surgical evaluation

One key to successful epilepsy surgery is accurate localization of the seizure focus, where seizures apparently start. Secondarily generalized tonic-clonic seizures will stop if the focal point of origin is removed. Temporal lobe is the most seizure-prone of the four lobes of the brain, although surgery can be performed in any lobe of the brain. Seizures that emanate from both temporal lobes are not amenable to surgery, because removal of both temporal lobes would create severe and permanent memory problems.

EEG (electroencephalogram, brain waves) can help to localize the seizure focus, by demonstrating abnormal electrical activity. Most EEGs are obtained between seizures. With a single EEG, abnormalities are seen in about half of people with epilepsy, but the percentage of significant findings increases with repeated EEG recordings, approaching 80% after four EEGs. Between seizures, EEGs
can show spikes or sharp waves. These are pointy waveforms reflecting hyper-excitability of the underlying brain. Surgical candidates usually undergo video-EEG monitoring in a hospital epilepsy monitoring unit in order to record brain activity and behavior during several seizures. The hope is to find that all seizures come from the same region (the seizure focus), and that it is located in a safe place for surgery. The most common location for a seizure focus is in the inner portions of the temporal lobe, deep to the left or right ear. Inpatient video-EEG monitoring can take from 1 to 14 days, depending on how soon seizures occur. Medications may be temporarily withheld to provoke seizures for recording. A personal account of video-EEG monitoring can be read at http://www.epilepsy.com/epilepsy/journal/issue1/video-eeg.

Magnetic resonance imaging (MRI) or computed tomography (CT) provide structural images of brain. MRI shows greater detail than does CT. These tests may show an underlying cause of the seizures, for example, abnormal blood vessels, an old stroke, scarring from a prior infection, a birth defect (called dysplasia), a tumor, or a form of scarring in the temporal lobe called mesial temporal sclerosis. However, MRIs fail to disclose a cause of epilepsy in more than half of cases. Every serious candidate for epilepsy surgery needs a high quality brain MRI.

Positron emission tomography (PET) scan is a neuroimaging procedure that looks at glucose (sugar) consumption in the brain. Glucose is the energy supply for the brain. The majority of people with a temporal lobe seizure focus demonstrate low glucose consumption in the region of a seizure focus. A PET scan is not required for every epilepsy surgery evaluation, but it can be helpful where the location of the seizure focus remains unclear after video-EEG monitoring and MRI.

Neuropsychological tests are performed to determine whether a patient has speech or comprehension impairments, usually reflecting injury to the dominant left brain (in right-handers), or picture, face and shape memory impairments, which usually reflects right brain damage. Neuropsychological testing also can screen for depression, which is highly prevalent in this population. Psychosocial adjustment after epilepsy surgery is important to the success of the procedure, since the goal is improvement of quality of life, rather than just elimination of seizures.

Other specialized tests, such as magnetoencephalography (MEG), magnetic resonance spectroscopy and cerebral angiography are useful in some particular circumstances, but not required in all cases.

Some patients appear to be surgical candidates, but the seizure focus cannot be precisely localized with the above tests. These individuals may undergo invasive monitoring with electrode wires placed into regions of brain suspected of harboring a seizure focus. Brain electrodes come in the form of thin wires to be be inserted into brain tissue or plastic sheets of electrodes, called strips or grids, to be place on top of brain tissue (figure). Each type is useful in different circumstances. Brain electrodes often show where seizures originate, but use of these electrodes does entail some risk for bleeding, infection or injury to brain. Grids can be used to electrically stimulate the area underneath the contact points and map the function of the brain at that region. This procedure is used when the seizure focus is likely very close to a speech or sensory-motor area of brain and precise delineation of boundaries is required. The grid usually is left in place for about a week. When it is removed, the operation to remove the seizure focus is done during the same procedure. Only a few percent of patients with epilepsy undergoing surgery will need mapping with a grid.

The Wada intracarotid hemispheric dominance test is done to localize speech and memory functions in candidates for epilepsy surgery. A portion of the brain on the left or the right is anesthetized by injection of a quick-acting sedative into the internal carotid artery, via a catheter placed in the femoral vein at the groin. Speech and memory then are tested. It can be thought of as a “dry run” for surgery. Surgery can be performed on the temporal lobe of the speech-dominant side, but not as much brain can safely be removed as on the non-dominant side. Extensive amnesia after injecting one internal carotid artery is a danger signal for surgery, because it suggests that there could be
severe memory problems after the operation. The Wada test usually does not require overnight hospitalization.

Upon completion of evaluation to localize the seizure focus, the patient, family, and doctor will discuss whether to proceed with surgery. Epilepsy surgery is elective; no person should be pushed into having epilepsy surgery. Alternatives include continuing with conventional anti-epileptic medications, trying new medications, vagus nerve stimulation, deep brain stimulation, the ketogenic diet, and other therapies currently being researched. Surgery may, however, be the most effective way to eliminate seizures in people whose seizures are not controlled by medications.

**Temporal Lobectomy Surgical Procedure**

Removal of the inner seizure-prone portions of the left or right temporal lobe is called partial temporal lobectomy, and it is the most commonly performed operation for epilepsy.

After the patient is positioned and asleep, the surgery begins. A patch of hair over the temple is shaved, but it is not necessary to shave the entire head (some prefer a full shave to an uneven trimming). Skin is cut in a “C”-shaped partial circle above the ear. Several nickel-sized holes are drilled in a circular pattern. A bone-saw cuts between the holes to remove a circle of bone about the circumference of a coffee cup. At the end of the procedure, this bone will be hard-wired back in place and eventually will calcify to seal to the skull. The membrane over the brain, the dura mater, then is opened, exposing the temporal lobe. Portions of the temporal lobe are removed by suction, since the brain has a soft consistency. Different surgeons use different techniques and approaches, depending upon preference and training, but no one technique is proven superior to the others. The amount usually removed ranges between the size of a golf ball and a small lemon, representing less than half the volume of the temporal lobe (figure).

The portion of brain removed never grows back. The space that it previously occupied immediately fills with the cerebrospinal fluid surrounding the brain. Patients sometimes wonder why replacing a seizure-producing scar with a surgical scar is beneficial. The reason is that not all scars are alike. The “clean” scar left by neurosurgery rarely leads to seizures. Closure of the surgical field occurs in reverse order to the opening.

Patients typically are in the operating room and recovery room for 6-8 hours, sometimes longer, with the operation itself requiring about 3-4 hours. The family should be prepared for the patient to be disoriented for a day postoperatively. Headache is common, but over-medication is avoided to allow the patient to wake up. Common postoperative side effects in the first few days include nausea from the anesthesia, a sore throat from the breathing tube in the operating room, swelling and bruising of the forehead and around the eye on the side of surgery. The swelling increases to a peak 2-4 days after surgery. An overnight stay in intensive care is common to provide close nursing monitoring. By 2-3 days after surgery, most patients are able to sit in a chair, walk with assistance, and eat. Seizure medicines may have to be given by vein until pills can be swallowed. Since not every medicine has an intravenous form, a temporary switch to one that does may be required. Hospital discharge happens 3-7 days after surgery. Patients should plan on staying at home with assistance for a week, and staying off work or heavy activities for a month. A few patients have persistent headache or fatigue, and require 2-3 months post-operative rest.
Complications of temporal lobectomy occur in about 2% of patients (one-in-fifty) who have this surgery. Complications can be serious, including as a partial list:

- Speech problems
- Reading difficulties
- Stroke, partial paralysis or numbness
- Personality change
- Deterioration of memory ability
- Partial loss of vision
- Depression, agitation, psychosis
- Death (0.1 – 0.5%)
- Others

Less serious complications occur more often, such as deterioration of word-finding ability for a few months after surgery, pain-itching around the skin scar (especially as it heals), infection of the surgical site, skull indentations or other cosmetic defects, persistent headaches, minor loss of upper peripheral vision on the side opposite the surgery, drooping of eyelid or forehead on the surgical side, transient depression, and a variety of other problems.

Seizures occasionally flare up for 1-2 months after seizure surgery, as the brain heals. Seizures during the postoperative months do not necessarily mean that the operation was a failure, since seizures may settle down with healing. You should discuss the potential benefits and risks of surgery with your surgeon, and give what is known as “informed consent” for the procedure if you agreed to have surgery.

Epilepsy surgery eliminates disabling seizures about two-thirds of the time, and produces partial improvement in an additional percentage. Patients may be completely cured of their epilepsy and be able to go off all medications, typically a year or two after the surgery. Others still require medication. Benefit of surgery may fall short of a complete cure - patients may still have occasional auras (warnings) or rare breakthrough seizures at times of great stress. Some patients do not respond favorably to seizure surgery, usually because not all of the focus could be removed or because the seizures were in fact located at several places in the brain (multifocal).

Other Surgical Procedures

Other specialized procedures are performed less often than is partial temporal lobectomy. The corpus callosum resection (colloquially known as the split-brain operation,) separates the major band of fibers inter-connecting the left and the right hemisphere of brain. This rarely cures seizures, but may slow down spread of the seizures and allow time for a warning in time to sit down. The split-brain operation can be viewed as a procedure to prevent injuries from seizures, rather than a cure for seizures.

Hemispherectomy entails removal of the majority of one hemisphere (half) of the brain. This radical procedure is employed in individuals, usually children, who have severe damage to one hemisphere. Candidates may suffer from a type of encephalitis called Rasmussen’s encephalitis, in which the local damage to a hemisphere is progressive over years. Although the children are initially weak on the side of the body opposite surgery after the procedure, function usually partially recovers. Recovery is more complete for younger children (< age 6) than for those in the teens or beyond. Children who recover well from a hemispherectomy grow up with only a clumsy hand and a limp.

Lesionectomy involves removal of a lesion, which is a visible structural abnormality causing the seizures, for example, a small tumor or an abnormal blood vessel. This procedure can be very effective in cases where the whole lesion and a small surrounding margin of brain can safely be removed.

Epilepsy surgery is a specialized type of neurosurgery. It has been performed at Academic Epilepsy Centers where a multidisciplinary team can evaluate and treat the patient. A list of such centers, certified by the National Association of Epilepsy Centers, can be found at http://www.naeclocator.org/locator/default2.asp.

Surgery Conclusion

Epilepsy surgery is sometimes a good option for people whose seizures cannot be controlled by medication. Temporal lobectomy is the most common epilepsy surgery procedure and lesionectomy the next. Each of these first requires tests to localize the place of origin of seizures in the brain. In properly selected candidates, epilepsy surgery can eliminate or greatly reduce seizures, and thereby allow reduction of seizure medication. Unfortunately, the success rate is not 100% and serious complications occur in about 1 in 50 people undergoing surgery for their epilepsy. Epilepsy surgery is always elective and it is not for everyone, but sometimes it is the best way to control seizures and improve the quality of life.

Videos on epilepsy surgery and interviews with people who have had surgery can be viewed at http://my.epilepsy.com/mmc/video.

The Ketogenic Diet
In the early part of the 1900's, a few people noticed that their children’s seizures improved during times of fasting. The ketogenic diet is designed to imitate the chemistry of the fasting state, by depriving the brain of sugar. The diet is very low in carbohydrates (bread, sugar, fruits, vegetables, etc.), and is very high in fat and protein. The resulting body chemistry changes make the brain more resistant to seizures. Although there have been some well-publicized dramatic successes from the ketogenic diet, the majority of people will not benefit from the diet. It seems to work best for children under the age of 12 with drop (tonic or tonic) seizures. Some adults also can benefit, if they stay on the diet. Partial adherence to the diet is not useful - it is all the way or nothing. Even one piece of bread will destroy the needed chemical changes for at least two days. Long-term safety of this diet has not been established. The ketogenic diet can raise blood fats and cholesterol, inhibit growth and weaken bones. In some cases, the diet can be stopped after two years and seizures do not return. The diet can be tried with anti-seizure medications, or on its own. The guidance of an experienced medical team is crucial. Families should not attempt this diet on their own!

Biofeedback for Seizures

Several types of biofeedback have been tried for control of seizures. In the simplest form, a machine is used to help people control their muscle tension or body temperature, which can lead to greater degrees of relaxation. Relaxation may help some people with seizures. Another form of biofeedback uses EEG machines to try to teach the patient to change some aspect of their brainwave pattern. Biofeedback is harmless, but has not yet been proven effective in scientific studies. Most insurance plans do not pay for biofeedback. A decision to try biofeedback must be individualized.

What Can a Person do to Control Seizures?

Most people can not stop their seizures. People can reduce their chances of having a seizure by regularly taking their seizure medications, avoiding sleep deprivation and staying in good general health. If trigger factors, such as alcohol or flashing lights are known, they should of course be avoided. No specific diet is known (other than the ketogenic diet described above) that reliably will stop seizures. Some people turn to natural remedies, also known as alternative medicines: herbs, acupuncture, homeopathy and allied treatments. A few people report that these treatments are useful, but others do not. Since they are not scientifically proven, each person must make his or her own decision about trying alternative medical remedies. Be aware that many “natural remedies” are in fact drugs by another name. Natural products containing stimulants (for example, Ephedra, ephedrine, or nightshade) can provoke seizures. You should not stop your standard seizure medications in favor of alternative treatments without discussing this with your doctor!

Vagus Nerve Stimulation

The vagus nerve is a nerve running from brainstem through the neck to lung, heart, stomach, bowel and other visceral organs. The vagus nerve is part of the parasympathetic, autonomic nervous system that regulates automatic functions such as breathing, heartbeat and digestion. Years ago, researchers discovered that stimulation of the vagus nerve could influence electrical activity (EEG) of the brain. Tests in laboratory models of epilepsy showed that vagus nerve stimulation reduced the likelihood of having a seizure. Human trials therefore were begun.

Stimulation of only the left vagus nerve causes few effects on breathing, heart or digestion, but still seems to produce some benefit against seizures. Clinical trials of left vagus nerve stimulation (VNS) showed an average of about 25% improvement in seizures. Over a year or two, this benefit may increase to about 50% improvement. Some patients find that the seizures that remain are less intense or prolonged. Responses vary with the individual, so that some may get no benefit from VNS, and others may have substantial benefits. Unfortunately, few people with medically-uncontrollable seizures will become seizure-free with VNS, and few can eliminate their medicines. Some can reduce their doses of medicines. The VNS is considered to be proven therapy, according to the FDA, Medicare and most insurance companies.

Implantation of a stimulator is done by a surgeon, usually as a simple (about 2 hour) outpatient procedure. The patient ends up with a stimulator pack about the size of a thin cigarette lighter above the left breast. A wire travels under the skin, over the collar bone to the left neck, where it wraps around the vagus nerve. Two scars result: one on the chest and one on the neck. No brain surgery is involved in the procedure; the vagus nerve in the neck is used as a route to feed electrical activity into the brain. The entire device is under the skin (subcutaneous), with no protruding wires. Batteries in the stimulator last from about 3 – 6 years, depending upon the intensity and frequency of stimulation. When batteries die, replacement is done by replacing the whole stimulating device on the chest, in another minor surgical procedure.
Early testing of VNS showed benefit against seizures lasting for 5-10 minutes. Therefore, clinical trials tested the VNS with the stimulation on for 30 seconds and off for every five minutes. Intermittent stimulation preserves battery life, and may be less irritating to the vagus nerve. However, some patients have more benefit with rapid cycling, such as on for 30 seconds and off for 30 seconds, or even on continuously.

The main side effects of VNS are hoarseness of voice when the stimulator is on and possible coughing or irritation of the throat. Problems with breathing, heartbeat, digestion or other autonomic nervous system problems can happen, but are surprisingly rare. Occasionally, the surgical site becomes infected or irritated. In general, VNS is quite safe and well-tolerated, lacking the side effects of many antiepileptic drugs. After implantation, the stimulator is turned up slowly. Stimulation current ranges from about 0.2 – 3.5 mA. Higher currents may be better against seizures, but also more irritating to the throat. Turning the current up slowly at two-week intervals can allow the patient to become used to the side effects.

Changes in the VNS current intensity or cycle time are done by a physician with by a paddle programmer held against the chest. No needles or discomfort are required to reprogram the stimulator. The patient cannot do reprogramming, but can turn the stimulator on or off at a given time by holding a strong magnet against the device. A few patients find that turning the VNS on at the time of a seizure warning is useful. Others may turn it off, by taping a magnet against the stimulator, for example, for the duration of a phone call, in order to avoid hoarseness. If a VNS is not helping, it can be removed by a surgeon.

VNS is not curative therapy, and so it is not a substitute for other epilepsy surgeries that have a good chance to cure. VNS make little sense if seizures are easily controlled by medicines. Our clinic finds the VNS most useful for people who do not respond to or cannot tolerate medicines, but who are not candidates for curative surgery. Partial (focal) seizures are the types of seizures most studied, but VNS may be useful for other types of seizures as well. In addition, studies are underway to evaluate possible benefit of VNS for depression, pain, headaches and various other conditions.

The Patient-Doctor Relationship

You should be comfortable with your medical team. Remember that they are working for you. Communication should be honest and open. A doctor can never guarantee a result; chances that a treatment will produce seizure control or side effects can only be expressed as probabilities. Seizures and side effects remain unpredictable.

Your doctor will rely on you to tell of unexpected problems from a treatment. You have to make a judgment as to whether a problem is minor and can wait for the next scheduled visit, or whether it is urgent, and requires immediate attention. If immediate attention is needed, then you should receive it from your doctor or from medical personnel covering for the doctor.

The most common complaint against physicians is that they do not spend enough time listening and explaining. This usually is because forces outside the doctor’s control limit visit time. Nurse clinicians can be a great help by gathering history and providing information. Many of them are very knowledgeable regarding seizures and antiepileptic medications. You should prioritize your questions and concerns, since not everything can be addressed in one visit. Several visits may be needed to cover all the territory. Recognize that your neurologist is a specialist, and can best be used for neurological problems, and not general medical problems. Do not hesitate, however, to ask if a general medical problem (for example, rash, joint pain, excessive fatigue, stomach upset, sexual dysfunction, etc.) is a possible side effect of the seizure medication. Sometimes it is, and this is within the expertise of a neurologist.

Most neurologists find seizure calendars helpful. Write down the dates and times of your seizures on a calendar or a piece of paper. If you have more than one seizure type, specify which you had. Note any possible triggering factors, for example, missing medications or the start of a menstrual period. Bring this information with you to clinic visits.

A doctor should never object to the forwarding of records to other doctors (although there may be a small charge for doing so), or to a second opinion. If you wish to change doctors, that is your right. You should not worry about offending your doctor; you are the customer, and your health is the key issue. Changing physicians does not mean that the physician is a bad doctor, but only that you and she/he do not have the right “chemistry” to work together well. Conversely, a doctor has the right to refuse to treat a patient, except in an emergency. In such instances, the physician should help you to determine where you can turn for help.

Social Issues in Epilepsy:
The most important issues for patients with epilepsy are social. Although physicians, in their clinic encounters with patients, talk most about seizure frequency, medication side effects, and results of testing, patients may have a different set of concerns. They want to know how to deal with the embarrassment of a seizure. They want to know how seizures are going to affect their ability to get or keep a good job, or succeed in school. They want to know what seizures will mean for their social life, marriage, a family, childbearing and raising. They want to know what seizures will do to their driver’s license and independence. Epilepsy is associated with considerable fear, misinformation and stigma. For obscure historical reasons, epilepsy is viewed by the public as a disorder linked to insanity, or in some cases even evil. Successful treatment of people with epilepsy requires an approach to these social issues.

Much discussion occurs about driving. People with frequent seizures should not drive, but people with infrequent seizures may be allowed to drive as a risk that is comparable to those taken with other medical conditions. Different states have different seizure-free intervals, varying from three months to two years. The shorter time intervals allow people with epilepsy to make other arrangements for work or driving, and theoretically encourage honesty in their reporting of seizures. People with seizures can obtain exemptions allowing driving if the seizures are restricted to times of sleep, or if the seizures have a prolonged and consistent warning that would allow someone to pull safely over, or if seizures are of a type that does not affect driving. Most states make it the responsibility of the person with epilepsy to notify the motor vehicle division. California is one of the six states that require seizure reporting by patients and doctors as a matter of law. Failure to report can result in criminal prosecution. Most physicians disagree with the required reporting, because it encourages dishonesty with the physician about the occurrence of seizures, which may prevent their adequate treatment.

**Employment**

What is the impact of seizures on employment? Most people with epilepsy can and do work, but having epilepsy doesn’t make it any easier, especially in the current economic climate. What do you need to disclose when you apply for a job? What are your rights if you are let go because of seizures or your employer’s fear of you having a seizure? Are there some jobs that you cannot do? Let’s take these questions one by one.

What to disclose? When you apply for a job, you do not need to reveal any medical conditions, medications or disabilities, unless the condition will make it impossible for you to fulfill the requirements of the job. Asking questions about a disability on an application form or in an interview is illegal. If you are asked, you can decline to answer or decide to seek work at a more informed and enlightened establishment. I recommend that you do not lie. If you do choose to disclose your epilepsy, it usually is best to do so in person at an interview, along with a discussion of how epilepsy will not limit your productivity.

What are your rights? Several federal and state laws pertain to rights of people with disabilities. The most relevant to people with epilepsy is the Federal 1990 Americans with Disabilities Act (ADA), authored by then Representative Tony Coelho, who is public about his own struggle with epilepsy. The ADA was amended in 2008 to clarify and extend who qualifies as being disabled. The ADA applies to businesses that employ 15 or more people, or who operate with Federal funding. Such businesses cannot discriminate on the basis of a disability. If a person with epilepsy cannot perform a job because of seizures or other limitations related to their disability, then the employer must attempt to make a “reasonable accommodation” for them within the framework of their employment. An accommodation might comprise a desk job instead of a driving job, or stable hourly shifts instead of changing shifts with sleep deprivation. An accommodation might include provisions for recovery breaks after a seizure. Before terminating an employee with epilepsy, an employer will need to be prepared to document attempts to arrange a reasonable accommodation.

If you believe that you have been discriminated against, you have three general options. The first is to talk to the Human Resources office of the company, which generally is fairly sophisticated about disability and discrimination issues. Perhaps, you are not hearing the official company view. The second is to contact the Equal Employment Opportunity Commission (http://eeoc.gov) in your region. The EEOC may, after hearing your story, decide to send a letter to or file an action against the company allegedly discriminating against you. Such actions typically are at no charge, but the EEOC may not choose to pursue your case. Your third option is to hire a disability attorney to advocate or sue on your behalf. This is a potentially expensive endeavor.

Can you do any job? The answer unfortunately is no, but well over 90% of jobs should not be limited by epilepsy. Absence of a driver’s license would prohibit employment requiring an on-the-road component. Some manufacturing or construction jobs - roofer, for example, might be unwise for someone with uncontrolled seizures. But the modern workplace has safety requirements to protect all workers, many of which will apply equally well to people at risk for having seizures. Such safety features might allow working around potentially dangerous machinery, chemicals, heat or on heights. Individualized judgment, and sometimes a three-way conversation among employee, employer and physician, is needed to decide whether the risks of the job are too high even
with safety features. In a large study of working people with disabilities by Zwerling and colleagues, published in 1997 in the Journal of the American Medical Association (volume 278, page 2163), 3 of 209 workers with epilepsy experienced on-the-job injury. This was 58% higher than the expected number, but not statistically different from the background risk rate. The message is that injuries can happen on (or off) the job in people with epilepsy, but the rate of injuries is not significantly increased.

Some work limitations may derive from side effects of seizure medicines that limit balance, energy, mood, memory, mental sharpness or ability to function under stress. A person with medication side effects should explore with his or her medical team whether a change in medications would make it easier to work. Epilepsy sometimes coexists with brain injuries that impose their own limits on potential for employment. In general, epilepsy does not mean unemployed; many people with epilepsy are outstanding employees.

School

Children with epilepsy can do well in school, but some do not. This may be because of social and peer pressure factors and factors of self-image and expectations. Other children have epilepsy because of an underlying injury to brain, and that brain injury may impair their ability to learn. Another major factor is anti-epileptic medications, which can impact negatively on learning and behavior. This is particularly true for barbiturate medications. A balance must be struck between the need for seizure control and the side effects of medications on schooling.

Pregnancy

Women with epilepsy can become pregnant, have normal children, and participate fully in parenthood. Pregnancies may be higher risk for women with epilepsy, because of the possibility of problems from seizures during pregnancy and because of effects of antiepileptic drugs (AEDs) on the fetus. The Epilepsy Therapy Project has had a special interest in this issue, and a few years ago established the Health Outcomes in Pregnancy and Epilepsy (HOPE) Forum with nine international working groups to identify important unanswered questions regarding epilepsy and pregnancy (http://professionals.epilepsy.com/page/ar_1191430420.html). Many questions remain, but enough is known to provide useful advice in several areas.

Planning: About half of pregnancies in the US are unplanned, but it is better for a woman with epilepsy to plan and prepare for pregnancy. Changing AEDs in the midst of a pregnancy can be problematic. If a woman has been seizure-free for 2-5 years, and does not have an ongoing condition predisposing to seizures, then it might be possible to eliminate seizure medicines prior to pregnancy. Short of removing all seizure medicines, streamlining to a few of the newer medicines, with lower birth defect risks, may be desirable. A period of at least six months before pregnancy is optimal to adjust medications. Certain seizures are very minor and may allow medication tapering for pregnancy; however, this requires caution, because more powerful seizures can emerge after tapering or reducing AEDs.

Fertility: Women with epilepsy have a slightly lower fertility rate than average. An irregular menstrual cycle and certain hormonal disorders, such as the condition called polycystic ovaries, can be caused both by seizures and by antiepileptic medications, especially Depakote (valproic acid). The desire to engage in sex (libido) can be reduced in association with epilepsy and also by AEDs. The rate of miscarriages is higher in women with epilepsy. Despite these risk factors, the large majority of women with epilepsy can become pregnant and carry the baby successfully to term.

Effect on contraception: The older seizure medicines, Dilantin, phenobarbital, Tegretol, and to a smaller extent other AEDs, can cause birth control pills, patches or injections to become less effective by inducing the liver to eliminate hormones faster from the bloodstream. This can result in unexpected pregnancy. Oral contraceptives containing the equivalent of 35 micrograms or less of the female hormone ethinyl estradiol are particularly likely to be rendered less effective by AEDs. AEDs do not affect efficacy of condoms, foams, IUDs or tubal ligation.

Birth defect risk: Birth defects occur at a rate a few percent higher in women with epilepsy than in the general population. The baseline rate of birth defects, large or small, is about 2% for American women. This birth defect risk increases to about 3-15% among women with epilepsy. Looked at positively, more than 90% of women will have healthy babies. Some contribution to the birth defect risk is made by seizures, and by underlying general health problems, but the main birth defect risk is from antiepileptic medications. This is known because birth defect risk is higher in women taking AEDs for conditions other than epilepsy. Risks are higher with consumption of multiple AEDs during pregnancy (polytherapy), compared to one (monotherapy).
The best AED to use during pregnancy has been debated, but no scientific study specifies a “safest” AED. There is, however, a growing belief that phenobarbital and valproic acid (Depakote) should be used with special caution during pregnancy. The US Food and Drug Administration (FDA) categorizes all medicines with respect to safety during pregnancy: A = has good evidence of safety during pregnancy; B = safety in animal studies; C = problems in animal studies, with uncertainty in humans; D = known to cause birth defects in humans, but benefits may outweigh risks; X = known to cause birth defects in humans, and benefits are unlikely to outweigh risks. The older AEDs, for example, Dilantin, phenobarbital, Tegretol, Depakote, are category D. The newer AEDs, for example, Neurontin, Lamictal, Topamax, Zonegran, Trileptal, Keppra, Lyrica, Vimpat, are category C.

Birth defects can cause a wide range of problems in the baby. Phenytoin (Dilantin) and barbiturates can cause cleft lip or palate, or other skull, face, or heart malformations. Valproic acid (Depakote) and, to a smaller extent carbamazepine (Tegretol, Carbatrol), are linked to open spine problems. Carbamazepine can cause “minor defects,” such as fingernail malformations, or mild facial feature distortions, that often resolve by age five years. Phenobarbital or valproate (Depakote) during pregnancy may affect future intelligence of the child, but this can occur with other AEDs as well. Many other birth defects are possible. The best rule is to use the single medicine that is most effective in treating the woman’s seizures, but with some bias toward the newer FDA category C antiepileptic drugs.

Folic acid: Supplementation with the vitamin folic acid (folate) 0.4-1.0 mg per day reduces risk for open-spine birth defects among populations of women without neurological disease. By analogy, most epilepsy doctors prescribe folic acid for women who might become pregnant while on antiepileptic medications. The best dose is not known, but quantities range from 0.4 - 5 mg per day. Most over-the-counter daily vitamins contain 0.4 mg (400 micrograms) of folic acid, and most prenatal vitamins, 1 mg. Folic acid usually produces no side effects but in high doses can lead to gastrointestinal or sleep problems, and a few researchers have speculated about heart or cancer problems for very high doses of folic acid. Women of child-bearing potential should take folic acid every day, since many women are not aware that they are pregnant during the critical first six weeks.

What to do during pregnancy: During pregnancy, women should be followed by their physicians, at best involving joint management by an obstetrician and a neurologist with expertise in epilepsy. Do NOT stop or change your seizure medications on your own – serious problems can result for you and the future baby. Occasionally, seizures may increase during pregnancy, but they are just as likely to improve or remain stable. During pregnancy, AED blood levels may change in a way to produce unexpected breakthrough seizures or medication side effects, and this should be monitored. Lamictal (lamotrigine) blood levels, for example, can decrease by more than half during pregnancy and increase within two weeks of delivery, if dose is not adjusted as needed. Decreased blood levels also can occur with Keppra, Trileptal and sometimes other AEDs. The usual pregnancy safety concerns also apply, such as good diet, judicious exercise, using only necessary medications, and avoiding alcohol and smoking. Obstetricians usually advise women to take their AEDs up to time of delivery. Seizures during delivery are rare, but if they occur, they can be treated by the usual medical methods.

Pregnancy registries: Several pregnancy registries track safety of AEDs. Participation is free and the registry will both provide you with information and help the epilepsy community to better understand the safety of AEDs during pregnancy. We recommend that you contact one of the registries if you have epilepsy and are pregnant. A list and links can be found at http://my.epilepsy.com/node/572. These include:

The Antiepilepsy Drug (AED) Pregnancy Registry www.massgeneral.org/aed 1-888-233-2334
The UK Epilepsy and Pregnancy Registry
http://www.epilepsyandpregnancy.co.uk 0800-389-1248 (UK)
EURAP’s www.eurap.org (for physicians)
The Australian Pregnancy Registry
http://www.epilepsyaustralia.net/Australian_Pregnancy_Register/Australian_Pregnancy_Register.aspx 1800-069-722 (Australia)
Gabapentin (Neurontin) Pregnancy Registry 617-638-7751
Lamotrigine (Lamictal) Pregnancy Registry
http://pregnancyregistry.gsk.com/lamotrigine.html 1-800-336-2176

Bleeding and vitamin K: Some of the seizure medications, for example, Dilantin, Tegretol or, phenobarbital, can cause the liver to metabolize blood clotting factors faster, leading to a bleeding tendency in the baby. This can be counteracted by vitamin K, so some doctors prescribe Mephyton (Vitamin K) 5 mg pills, two pills per day for the final month of pregnancy. However, no large scientific study has validated this practice. Babies usually receive a vitamin K injection after birth.

Breastfeeding: Breastfeeding is beneficial, and the benefits usually outweigh the risks from trace amounts of seizure medicine present in the breast milk. The mother should recognize that the child already has been exposed for nine months to the medicine in the placental bloodstream. AEDs that are
highly bound to blood proteins, including Dilantin, phenobarbital, Tegegretol and Depakote do not significantly travel into breast milk; others, for example Keppra, Mysoline and Zonegran, do have measurable concentrations in breast milk. Rarely, a child may have side effects such as drowsiness or failure to thrive from seizure medications in breast milk, and then should be switched to formula feedings.

Caring for the baby: If a mother’s seizures are not in control, special care should be taken to avoid injury to the baby during lapses of attention. Change the baby’s diaper on the floor. Do not leave a baby in bathwater, on heights, near heat or other dangerous objects or chemicals. Find a safe method to carry the baby. Do not drive, with or without the baby, if your seizures are uncontrolled and may affect safety on the road.

Will the baby have epilepsy? Most children of mothers or fathers with epilepsy do not develop epilepsy, although the risk is slightly higher. A child in the general population has about a 1% risk of developing epilepsy. Children of mothers with epilepsy have a 3-9% risk, while children of fathers have a 1.5-3% risk. Still, the actual risk depends upon the specific type of epilepsy. Women with the category of epilepsy called primary generalized (with absence, initially generalized tonic-clonic and myoclonic seizures) are more likely to have children with epilepsy than are those with partial (focal) seizures.

Conclusion, pregnancy: Most women with epilepsy can become pregnant, carry a child successfully through pregnancy, breastfeed and be terrific mothers. For a minority of women with severe and uncontrolled seizures, or major accompanying medical problems, having children may be a poor decision. Planning is key, since medication changes during pregnancy can be risky. Folic acid should be taken by all women who may become pregnant. Some of the antiepileptic drugs can make hormonal contraceptives less effective. During pregnancy, keep in close touch with your doctor and do not change medications on your own. Here are some general suggestions regarding epilepsy and pregnancy, but take specific action based upon consultation with your personal medical team.

- Plan ahead and optimize medications
- Recognize possible effect of seizure medicines on contraception
- Do not change AEDs without talking with your doctor
- Take folic acid if you might become pregnant
- Have AED levels monitored more closely during pregnancy
- Your doctor may give vitamin K in the final month
- Breast feeding is usually OK
- Participate in a pregnancy registry

- Take safety precautions in caring for the baby

Risks of Epilepsy

Seizures entail some risk, as does the treatment or prevention of seizures. You should be aware of these risks, so that you can minimize them. If you wish to talk to someone about seizure safety, please contact your medical care team, since advice should come from someone who knows you.

Driving

Every State restricts driving in people with seizures. States typically require that you be seizure free for either 3, 6, 12 or 24 months from the date of the seizure (3-12 in California), depending on circumstances and doctor’s recommendations. The Department of Motor Vehicles (DMV), not the doctor, makes the decision on driving in most states. Exceptions can be made for seizures that do not affect mental condition and ability to control a car, or that occur 100% during sleep. Longer restrictions may apply for commercial driving. The DMV sometimes requires a road test and a fee to reinstate the license after a medical suspension. California, Nevada, Oregon, Pennsylvania, Delaware and New Jersey laws require that medical personnel report a diagnosis of epilepsy to the State authorities, although it is not usually required to report every seizure after initial reporting. The patient also has a personal legal obligation to report seizures to the DMV. We recommend:

- Do not drive if you are having seizures that would be dangerous on the road.
- Be honest with your doctor about your seizures. Safety comes first!
- Be honest with the DMV (use their driving form). It may protect you legally if problems later occur.

Water Safety

You could drown during a seizure that occurs in water. Use the buddy system for swimming. Let the buddy know that you have seizures. Take showers instead of baths. If seizures are frequent, buy a plastic shower chair and a flexible water hose.

Burn Safety

If you have uncontrolled seizures, be very careful around heat or flames. Cook on the back burner - you are less likely to lean on the burner or turn over the soup during a seizure. Don’t smoke, which is good advice for other reasons as well. Set the maximum house hot water temperature to 110 degrees Fahrenheit. Put guards on open fireplaces, wood stoves or radiators.
Heights

Occasional use of ladders and going up and down stairs is a reasonable risk. If your seizures are not in control, then do not work on ladders or unprotected heights for more than brief minutes. If you fall with some of your seizures, then fall-proof your environment. Put in carpets, cover sharp corners, and consider wearing a protective helmet in some circumstances.

Equipment and Power Tools

Cutting, chopping and drilling equipment should have safety guards to avoid inadvertent injury; otherwise, do not use it if your seizures are not fully controlled. Do not use mowers lacking automatic stop switches. Do not use chain saws.

Child Care Safety

If you have uncontrolled seizures, do not carry your child in your arms, but use one of the slings/papooses. Change the baby on the floor. Do not bathe the baby in water deep enough for the mouth to be underwater. Breastfeeding is usually considered beneficial, even though small amounts of seizure medicines come out in the breast milk.

Sudden Unexplained Death in Epilepsy (SUDEP)

It is rare for people to die from a seizure, but it can happen. One way is trauma or a car crash from a seizure. Another is the poorly understood condition called sudden unexplained death in epilepsy (SUDEP). We think this is most likely due to heart arrhythmias (irregular beats) or breathing problems caused by a seizure, but the mechanism is debated. For people with uncontrolled seizures we recommend:

- Do not suddenly stop your seizure medication, since this can be a risk factor for SUDEP.
- Do not be overly worried about SUDEP. It is tragic when it happens, but it is uncommon and there are currently no preventive measures other than working toward the best seizure control.

Medication Side Effects

To be approved for prescription use, seizure medicines must pass strict safety testing. Nevertheless, they all have side effects, some of which are potentially serious or even lethal. The risks of medications must be balanced against the risks of seizures. A full discussion of possible medicine side effects is not possible here, but we recommend:

- Know the main side effects of your seizure medicines. Your doctor is the best source for individual information. Web sites such as epilepsy.com or epilepsyfoundation.org or the website of the drug manufacturer have good information.
- The package insert provided with your prescription lists full information on side effects, but most of these will never occur in an individual. Let the package insert inform you, but not scare you. Be aware that some side effects occur from drug interactions among all your medications. Interactions can involve prescription medicines, over-the-counter medicines, herbal remedies and even some foods. Grapefruit juice is an example of a seemingly benign food that can raise levels of carbamazepine or other drugs.
- Generic medications are less expensive, but may not produce the same blood levels as do brand name drugs or even other generics. Insurance plans and pharmacies sometimes switch to generics without patient or doctor approval. Be cautious if you are switching or being switched to generics. It may work out fine (and it often is a lot less expensive), but a blood test to check levels might be useful.

Seizure medicines and suicide

Seizure medicines have long been known to help some people with depression, but also to make others worse. The FDA recently took a look at their database of clinical studies of people taking epilepsy medicines. Their finding was 4 suicides in 27,863 patients taking epilepsy medicines, versus none in patients taking placebo (an inactive pill). They reported 105 people of the 27,863 who did not commit suicide, but had thoughts of suicide. Combined, the risk for suicidal thoughts and behavior was about 0.4% (1 in 250) for those taking epilepsy medications and 0.2% (1 in 500) for those given placebos.

This is important information because doctors and patients need to know the possible side effects of medicines. But it needs to be put in perspective and certainly is no reason for panic. The 4 suicides in 27,863 is a very small percentage, and it is impossible to be sure the epilepsy drugs were the cause. Depression occurs in about 10% or more of people with epilepsy, even independent of medications. We recommend the following:

- Do not stop your seizure medicine. It could be dangerous.
- If you have symptoms of depression, such as crying and low mood, please discuss them at your clinic visits, so a decision can be made about whether antidepressant medication or referral to a psychotherapist would be useful.
- If you are thinking seriously about suicide, call your medical providers immediately, or call 911.
- For most people, this FDA warning is just something to know, but not a reason to change medicines.
Carbamazepine in Asians and Rash Risk

Carbamazepine (Tegretol, Carbatrol) can cause an allergic rash in susceptible individuals. Sometimes this rash becomes severe, with swelling of the mucous membranes around mouth, eyes or genitals, or blistering of the skin. In these cases, the rash is called the Stevens-Johnson syndrome (SJS). Recent research shows that people of Asian descent have a higher risk for SJS from carbamazepine. Risk is increased with a genetic marker on blood cells called HLA-B*1502, which can be tested for in a blood test. About 15% of people from China, Taiwan, Philippines, Malaysia or Indonesia have this marker, versus 3% in people from India and 1% in people from Japan or Korea. People of Asian descent can be screened before starting carbamazepine. If someone has been on carbamazepine for 3 months already, there is said to be little risk of SJS. Further studies might indicate a similar situation for other antiepileptic drugs - we do not yet know. We recommend the following.

- If starting carbamazepine and you are of Asian descent, raise this issue with your doctor, and you and your doctor will decide what to do.
- If you have been taking carbamazepine for at least 3 months, there is no need to worry.
- Do not suddenly stop your seizure medicines.

Folic acid to protect from birth defects

Seizure medications can increase the risk of birth defects from a baseline risk of about 2% to a risk in the range of 4-15%. One of the common types of birth defects is a malformed lower spinal column (spinal bifida), potentially resulting in walking and bowel-bladder problems. The vitamin folic acid (also called folate) can decrease this risk in a general population of childbearing women. We do not have studies proving benefit specifically in women taking epilepsy medicines, but we think it reasonable to give folic acid to women with epilepsy who might become pregnant. It is best for folic acid to be in the woman’s system from the start of pregnancy, which means taking it all the time. From 0.4 - 4 mg per day in a single daily dose is the usual range. An over-the-counter multiple vitamin usually has 0.4 mg (400 micrograms) of folate. Doses of 1 mg and over require a prescription. Side effects are rare, but can include stomach upset or concentration problems. We recommend:

- Do not stop your seizure medications because of this issue.
- If you might become pregnant and you are taking seizure medicines, discuss taking folic acid with your medical team.

Birth control pills

Some seizure medicines lower effectiveness of birth control pills, which can result in unexpected pregnancy. These medicines include phenytoin (Dilantin), carbamazepine (Tegretol, Carbatrol), oxcarbazepine (Trileptal), phenobarbital and primidone (Mysoline), and rarely lamotrigine (Lamictal) and topiramate (Topamax) in high doses. The negative effect of seizure medicines on birth control pills is more likely with low-dose birth control pills: those containing less than the equivalent of 50 micrograms of ethinyl estradiol. We recommend:

- Do not stop your seizure medicines or your birth control pill because of this issue.
- If you are taking birth control pills and seizure medicines, confer with your neurologist, gynecologist or primary care doctor to make sure the dose of the BCP is adequate.

Bone health

Several of the older antiepileptic medications may cause thinning of bones with long-term use, leading to broken bones later in life. This is most problematic with phenytoin (Dilantin), but may occur with carbamazepine (Tegretol, Carbatrol), phenobarbital, primidone (Mysoline) and possibly valproate/valproic acid (Depakote, Depakene). This is a larger concern for women in mid-life or older, but it also can be an issue for men and younger women.

- This potential problem is not an emergency and occurs over months to years; do not stop your seizure medication without discussing your concerns with your doctor.
- Calcium, vitamin D3 supplementation and regular exercise may be helpful to maintain bone health. Your doctor may recommend other medications for bone health as well.
- Periodic bone density screening may be helpful to show existence or progression of bone thinning.

Recreation

If having a seizure during a recreational activity would cause you significant harm, then do not do the activity. Use common sense. Confer with your medical team for individual restrictions. As a general guideline for starting discussion with your medical team, we recommend:

- Low-risk recreation usually can be done by most people with seizures, even if the seizures are not in control. These include walking, running, bowling, golf, baseball, basketball, soccer, volleyball, swimming with the buddy system, weight training with machines or spotters, elliptical trainers, treadmills with spotters. Confirm this with your medical care team.
- You should be able to go at least 3 months without a seizure to participate in medium-risk activities, but confirm this interval with your doctor. These include...
football, hockey, ice skating, bike racing, gymnastics, horseback riding and boating.

- You should be seizure free for more than a year to perform high-risk activities, although some doctors recommend not ever engaging in high-risk recreational activities if you have epilepsy. Ask your medical team whether it is safe to engage in high-risk recreation. High-risk activities include hang gliding, motor sports, skiing, competitive skateboarding, mountain or rock climbing and SCUBA diving.

**Safety Proof Your Environment**

Arrange your home and if possible, work or study space, to be safe should you have a seizure. Pad sharp corners, include a non-trip/non-slip carpet, put barriers in front of fireplaces or hot stoves. If you wander confused during or after a seizure, pay special attention to heights, railings and nearby pools or bodies of water.

**Develop a Seizure Safety Plan**

Plan ahead for what you and family should do during a seizure. You can find a worksheet to construct a plan on [www.epilepsy.com](http://www.epilepsy.com).

And remember: safety first! Prevention of injury is better than treatment.

**For more Information**

The Epilepsy Therapy project provides [www.epilepsy.com](http://www.epilepsy.com), the world’s most visited website for information about epilepsy. An excellent source of information is the Epilepsy Foundation (of America), 301-459-3700, [www.epilepsyfoundation.org](http://www.epilepsyfoundation.org). The Northern California branch of the Foundation is the Epilepsy Foundation of Northern California 510-893-6272 or 800-632-3532, [efnca@epilepsynorcal.org](mailto:efnca@epilepsynorcal.org). The Stanford Comprehensive Epilepsy Center can be reached at 650-725-6648.

A tremendous amount of research is focused on the diagnosis, prevention, treatment, and cure of epilepsy. If you wish, you can help with this effort, and become involved in the Epilepsy movement, by contacting one of the above sites.