

OVERVIEW OF EPILEPSY

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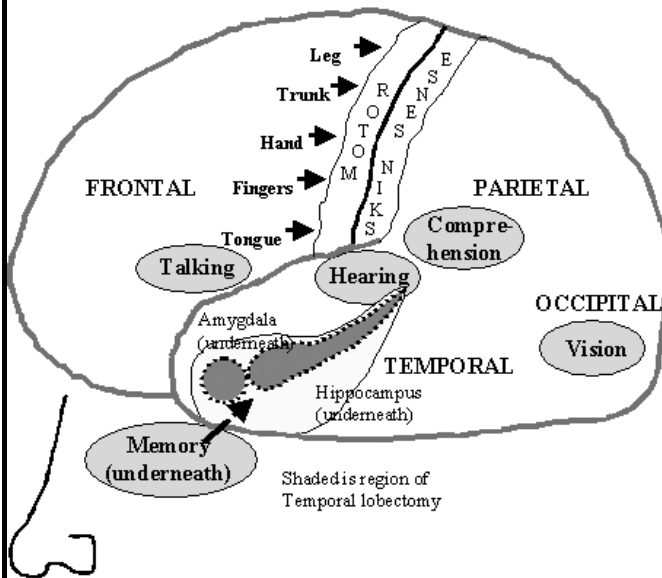


Figure 1: Brain Regions

DEFINITION AND MECHANISMS OF EPILEPSY

A seizure is a sudden stereotyped episode with change in motor activity, sensation, behavior, emotion, memory or consciousness due to an abnormal electrical discharge in the brain. Epilepsy is a condition of recurrent spontaneous seizures. 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 lefties. 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 "grand mal convulsion" results, with loss of consciousness, stiffening and jerking.

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 in one particular part 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 all over the brain. In fact, epilepsy specialists believe that generalized seizures originate in deep structures of the brain and simply project to the cortical surface where we can see the manifestations of the seizure emerge relatively simultaneously.

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 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 are divided into several categories as listed in Table 1. 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 1:

SIMPLIFIED INTERNATIONAL CLASSIFICATION OF SEIZURES

Partial Seizures (Focal, start in one place)

Simple (no loss of consciousness/memory)

Sensory

Motor

Sensory-Motor

Psychic (abnl thoughts / perceptions)

Autonomic (Heat, flushing, GI)

Complex (loss of consciousness / memory)

With or without aura (warning)

With or without automatisms

Secondarily generalized (spreads)

Generalized

Absence, typical or atypical (petit mal)

Tonic-Clonic (grand mal)

Myoclonic

Atonic

Tonic

Unclassifiable

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.

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 are different. Patients with 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.

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.

Amyoclonic 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 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.

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.

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 THE 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 in-

cludes, 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 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 hypsarrhythmia, with high voltage spikes and a disordered high-voltage background. Early and vigorous treatment of the seizures with the corticosteroid 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 (not marketed in the US), felbamate, lamotrigine, and topiramate appear to have a possible role in treatment of infantile spasms.

Lennox-Gastaut Syndrome

The Lennox-Gastaut syndrome, a symptomatic generalized epilepsy, is a relatively rare disorder with the following criteria: 1. Multiple seizure types, usually including atonic or tonic seizures; 2. Variable degrees of cognitive 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 showing 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 seizures and prevent injuries. Valproate, benzodiazepines, lamotrigine, vigabatrin, topiramate, zonisamide, levetiracetam, and felbamate have been tried in this condition, 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 partial epilepsy, but there is no good evidence that trying to prevent febrile seizures reduces this risk. The large majority 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 personality. Phenobarbital 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 phenobarbital produces hyperactivity, behavior and learning problems in a significant fraction of children. Many pediatric neurologists believe that treatment of febrile seizures is worse than the occasional 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

Benign Rolandic epilepsy (BRE) is a seizure type usually appearing in children or adolescents, around age 6 to 16 years old. It represents an idiopathic localization-related epilepsy. The Rolandic region is the area of the brain at the frontal-parietal, motor-sensory junction. Seizures 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 is very good. Depending upon severity of seizures, BRE may or may not be treated with antiepileptic medications.

Juvenile Myoclonic Epilepsy

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

CAUSES (ETIOLOGIES) OF SEIZURES:

Anything that injures a region of the brain can lead to a seizure focus, but in more than half of cases no such injury or cause for the seizures can be identified. We infer the presence in such cases of a subtle injury or an imbalance of excitatory and inhibitory neurotransmitters in the brain. The type of injury that may lead to a seizure is age-dependent. Seizures originating in children often are caused by birth traumas, infections such as meningitis, congenital abnormalities, or high fevers. Seizures in the middle years commonly are caused by injuries from head trauma, infections, alcohol, stimulant drugs, or side effects of medication. Pregnant women can have seizures from eclampsia (toxemia) and related conditions. In the elderly, brain tumors and strokes cause a higher proportion of seizures. Nevertheless, any cause can produce seizures at almost any age, and the most common etiology (cause) at any age remains unknown. The medical term for unknown is "idiopathic."

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%.

Head Trauma

Head trauma is epidemic in our Society and is a common cause of epilepsy. Nevertheless, most people who have head trauma do not get epilepsy. The head trauma must be severe enough to injure the brain. This usually requires head trauma severe enough to produce coma or amnesia for many hours, or penetrating injuries to the brain. Being stunned, or experiencing brief losses of consciousness, which happens to almost everyone at some time in their life, usually does not lead to epilepsy. A seizure at the time of head trauma does not necessarily mean that seizures will continue chronically. In such cases, the medical team may choose to treat with anti-seizure medicines for a short period of time, or take a “watch-and-wait” attitude to see if seizures return. Epilepsy after head trauma can be delayed, sometimes by a few years. This is probably because the brain cells take time to grow new connections to replace the ones that were lost with the injury. The new connections can be hyper-excitabile and prone to seizures. Fig. 2 shows an MRI with bilateral frontal bruising (the white at the top of the brain) from severe head trauma.

Fig. 2: MRI of severe frontal brain trauma

Brain Tumors

Brain tumors are a rare, but troublesome, cause of seizures. Brain tumors can be benign or malignant. Examples of benign tumors are meningiomas, low-grade astrocytomas (Fig. 3), oligodendrogliomas, and gangliogliomas. More malignant tumors are high-grade astrocytoma, glioblastomas, lymphomas, and metastatic carcinomas to the brain. The prognosis and treatment of brain tumors is beyond the scope of this manual, but it is fair to say that treatment is individualized by a combination of surgery, radiation therapy (X-ray therapy), chemotherapy and many new promising experimental therapies.

Both benign and malignant brain tumors can cause seizures. The seizures usually are focal (partial), with a character that depends upon where in the brain the tumor resides. Seizures usually do not originate from tumor cells themselves (there are a few exceptions), but from the irritated brain surrounding the tumor. As with any seizure, the type of seizure depends upon location in the brain, for example, face twitching if the tumor is in the face area of the motor cortex. Focal seizures from tumors can be very difficult to treat. Sometimes the best that can be done is to keep the seizure from developing into grand mal infection in the brain can be cause of epilepsy. Children or adults may develop bacterial,

fungal or viral infection of the lining of the brain and spinal cord, called spinal meningitis. If the brain is itself infected, then the condition is called encephalitis. A brain infection with a walled-off area and pus inside the wall is called a brain abscess. All of these infections are potentially serious, and may leave brain scars and recurrent seizures in their wake. The Herpes virus is especially prone to cause seizures when it invades the brain. The AIDS virus can also produce seizures. When a person has a brain or suspected brain infection they are placed on antibiotics to treat the infection. They may also need seizure medications to control any seizures that occur at the time of the infection, or after the infection has left an injury scar on the brain.

If the tumor can successfully be treated, then the seizures usually improve. Patients should know that removal of all or most of a brain tumor by surgery or treatment with X-rays or chemotherapy will not necessarily completely cure the epilepsy, which originates from brain cells in the neighborhood of the tumor. Therefore, anti-seizure medications can be required for a long time. In a patient with a brain tumor, an unexplained deterioration in the seizure pattern calls for a re-evaluation of the condition of the tumor.

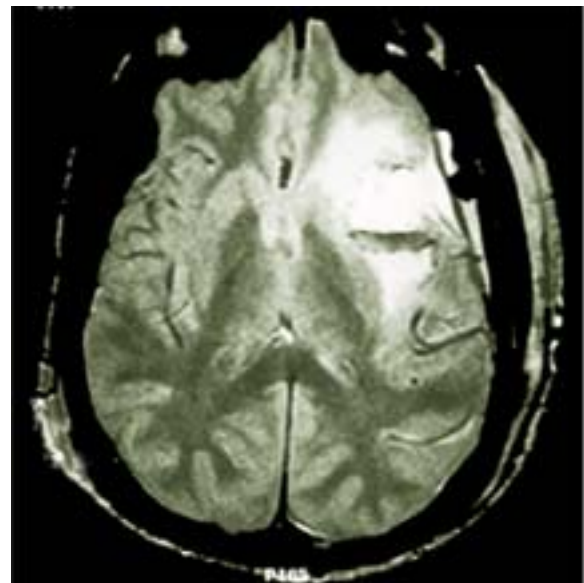


Fig. 3: MRI of brain tumor (astrocytoma)

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Infections and Seizures

A

Cysticercosis is an infection resulting from the pork tapeworm. By eating undercooked pork, or by contact with food or human waste containing the worm, people can become infected. The tiny worms travel through the intestines, to muscle and brain. There they form inflammatory cysts and die. Seizure can result from live or dead worms, but most seizures attributed to cysticercosis are from infections in the past. CT scans or MRIs may show calcium deposits at the place of prior cysts. Cysticercosis may be the most common known cause of seizures in the world, but it is much more common in the under-developed world than in the US. Seizures from cysticercosis are treated with the usual seizure medicines. If the infection is acute, then antibiotics such as praziquantal or albendazol and anti-inflammatory medications may be used.

Stroke and seizures

A stroke is caused by a blockage or loss of blood flow to portions of the brain. Strokes are more serious than seizures, since brain cells die during a stroke, whereas they do not during typical seizures. A stroke is caused by a blockage or loss of blood flow to portions of the brain. Strokes can happen to anyone, but they are more common in the elderly, in people with high blood pressure, heart problems, high cholesterol and clogged arteries. When a stroke injures, but does not kill, brain cells then those brain cells may become prone to generation of seizures. These seizures can be focal, depending upon the stroke location, or generalized grand mal, if the seizure discharge spreads throughout the whole brain.

Strokes can be obvious if they lead to sudden loss of strength, vision, or speech. Many strokes are not so obvious, because they are small or in the so-called silent areas of brain. People can have small strokes without knowing that they have had them. Still, such small strokes can generate a seizure focus in the brain.

Seizures from Dysplasias

A dysplasia is a group of normal brain cells that reside in an abnormal place in the brain. Other terms for dysplasias are dysgenesis, migration abnormalities, heterotopias and developmental defects. As the brain is formed in the womb trillions of neurons (brain cells) move from a central tube to a variety of different places in the brain. The signals that tell cells to go where they should are under intensive study, but are not fully understood. Some brain cells appear to get the wrong instructions and end up only part of the way to the cortex. In effect, they get off the elevator too soon. Since these cells are not surrounded by their usual neighbors, they are not subject to the normal inhibitory controls that neighbor brain cells normally exert. The cells of the dysplasia become hyperexcitable and produce seizures. Dysplasia is much more common than we used to think. Dysplasias usually are not

visible on a CAT scan, but may be visible on a high quality MRI. We believe that some small dysplasias are invisible, but are still large enough to cause seizures. Treatment of dysplasias is with seizure medications, or sometimes surgery to remove the dysplasias.

Seizures from Chemical Imbalances

Not all seizures result from a structural problem in the brain. Chemical imbalances also can cause seizures in a brain that looks perfectly normal on an MRI scan. Common chemical imbalances that can produce seizures can be caused by: alcohol, cocaine, stimulant street drugs or medications, antihistamines, certain antibiotics, aminophylline, some psychiatric medications, low blood sugar, low oxygen, low blood sodium (salt), low blood calcium, kidney or liver failure, complications of pregnancy, and many other conditions. Your doctors will evaluate you for these imbalances by a careful history and blood tests.

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, digoxon (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).

Hormonal factors and epilepsy

Some women notice a connection between their menstrual cycle and the likelihood of having a seizure. Pregnancy is a time when seizures occasionally become either worse or better. Seizures sometime come on or deteriorate at the time of puberty and may improve with menopause. Female hormones, particularly estrogen and its relatives, are known to have a role in regulating the level of brain excitability, and the link between hormones and seizures is real. Unfortunately, medical science has not yet been able to develop a treatment to alter this hormonal balance in a way that is useful for long-term seizure control. This is an active area of current research.

Women with epilepsy usually can take birth control pills or replacement hormones without worsening their seizures, but a few women are sensitive to hormone

changes. Women who take birth control pills should be aware that some seizure medications (phenytoin, carbamazepine, phenobarbital, topiramate, zonisamide; but not valproic acid, gabapentin, lamotrigine, or levetiracetam) reduce the effectiveness of birth control pills by causing the liver to clear them more rapidly from the bloodstream. Woman on seizure medicines that lower effectiveness of birth control pills require a high dose of estrogen to avoid pregnancy, namely an amount equivalent to at least 50 micrograms of ethinyl estradiol.

EPIDEMIOLOGY (THE NUMBERS) OF 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.



Fig. 4: historical figures with epilepsy

Many famous people in history have had epilepsy: **World Leaders:** Roman Emperor Julius Caesar, Peter the Great Czar of Russia, Napoleon, US President James Madison, Alexander the Great, Charles V King of England. **Religious figures:** Joan of Arc, Saint Paul the Prophet. **Writers:** Dostoevsky, Flaubert, Moliere, Jonathan Swift, Poet Lord Byron. **Composers and artists:** Handel, Tchaikovsky, Vincent Van Gogh. **Scientists and inventors:** Alfred Nobel - inventor of gunpowder and establisher of the Nobel Prize, Pythagoras, inventor of geometry; Socrates, Greek philosopher.

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, Tranxene, Librium). Commonly used medications or drugs that can lead to seizures in susceptible people include stimulants such as cocaine or diet pills, antihistamines, certain asthma medications (aminophylline), antidepressant medications (amitriptyline and relatives), major tranquilizers (Thorazine, Haldol, Mellaril, Stelazine and relatives), and some antibiotics (Flagyl, Cipro, and others). There is no scientific evidence that caffeine, cigarettes, or Nutra-Sweet (aspartame) causes seizures, but a few people may claim individual sensitivity. People report individual and highly unusual provoking factors, for example, 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, especially if the seizure is more than a day after the supposed trigger, or if the seizure only happened on one occasion after the trigger.

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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.

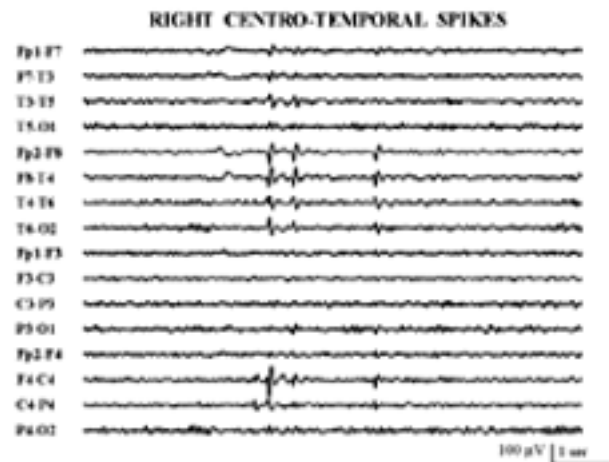


Fig. 5: EEG of interictal spikes

Absence (petit mal) seizures have a pattern known as “spike-waves” with spikes and after going slow waves (Fig. 6).

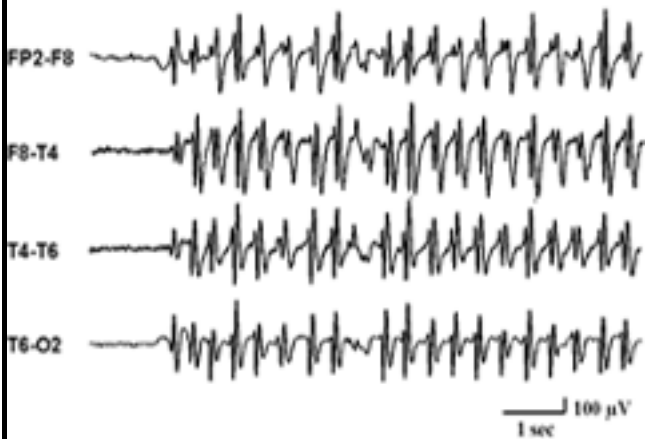


Fig. 6: EEG of spike-waves

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.

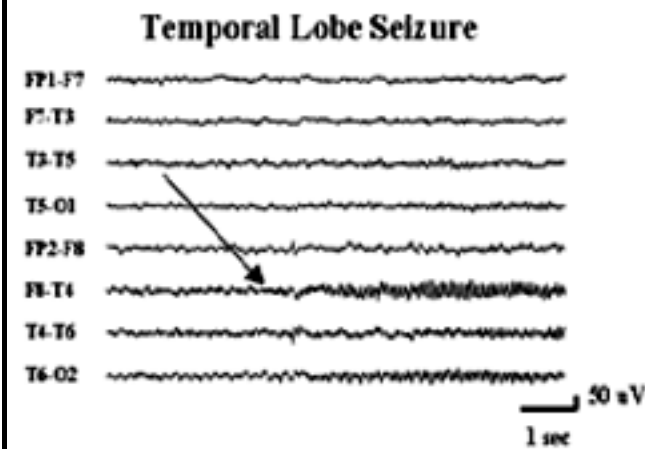


Fig. 7: EEG of a right temporal seizure (arrow)

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.

IMITATORS OF EPILEPSY:

Several conditions can result in abnormal movements, sensations, or loss of awareness, but not be associated with the abnormal electrical discharge in the brain. These are imitators of epilepsy.

Fainting spells or syncope may incorrectly be considered seizures. Typically, there will not be a prolonged period of jerking with such an episode. Interruptions of brain circulation produces symptoms that can be similar to those of epilepsy. Hypoglycemia (low blood sugar) or hypoxia (low oxygen) can cause confusional episodes that look like seizures. Some patients have confusional spells with bad migraine headaches. This may be mistaken for a seizure. Sleep disorders with inappropriate falling asleep such as narcolepsy or sleep apnea may look like seizures. Patients sometimes have movement disorders with tremors, nervous tics, dystonic posturing, or other forms of abnormal movement such as in Huntington’s chorea. These episodes may be thought to be simple partial motor seizures.

TABLE 2: IMITATORS OF EPILEPSY

- Syncope (fainting)
- Transient ischemic attacks (TIAs)
- Cardiac arrhythmias
- Hypoglycemia
- Hypoxia
- Confusional migraine
- Sleep disorders (e.g., narcolepsy)
- Vertigo
- Tremors, tics, dystonias
- Panic attacks
- Hyperventilation spells
- Night terrors
- Non-epileptic seizures (psychogenic, pseudoseizures)

Non-Epileptic Seizures

The most difficult imitators of epilepsy are the psychological imitators. Panic attacks, hyperventilation spells, and psychologically-based seizures can provide real diagnostic difficulties. Breath-holding spells are variants of temper tantrums in children. The child becomes angry, holds his or her breath, turns blue, loses consciousness and exhibits some jerking. Night terrors are screaming episodes during sleep in children. These last two conditions are alarming, but benign.

Psychological seizures also called psychosomatic seizures, pseudoseizures, psychogenic seizures, or non-epileptic seizures, are common in epilepsy centers. Subconscious stress causes the patient to have seizure-like episodes. A non-epileptic seizure does not reflect conscious “faking” of a seizure, but a subconscious psychosomatic stress reaction. Some patients with non-epileptic seizures have a background, even years before, of physical, emotional, verbal, or sexual abuse. Others are under certain hard-to-recognized causes for stress. Video-EEG monitoring usually is needed to secure a diagnosis of psychogenic seizures, since the expected EEG changes during a seizure will be absent. The treatment for these is psychological counseling and behavior modification therapy, not antiepileptic medications.

Imitators of epilepsy can be very difficult to distinguish from seizures. Some patients have been on antiepileptic medications inappropriately for decades for conditions that are not and never were seizures.

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 3

PRINCIPLES OF AED THERAPY
Decide whether to treat
Decide how long to treat
Use monotherapy where possible
Use simple regimens
Encourage compliance
Choose the best drug for a seizure type

The first principle is to decide whether to treat. Certain simple partial seizures with minor sensory, motor or thought activity might not require treatment. Even absence seizures or seizures of a partial complex nature might not require treatment, provided that they did not bother the patient, cause falls or injuries, and the patient did not wish to drive or work in potentially injurious conditions. A sin-

gle seizure might not require treatment since about 50% of people who have a single idiopathic generalized tonic-clonic seizure, with negative EEG, MRI and blood tests, will not have another seizure. By the second seizure, most epilepsy specialists would initiate treatment.

Antiepileptic therapy is not necessarily for life, but it can be. Under some conditions, medications safely can be tapered. This is particularly true if a patient has been seizure-free for at least 2-5 years, has no underlying structural lesion, does not have a genetic condition such as juvenile myoclonic epilepsy predisposing to ongoing seizures, has not had problems with status epilepticus, and has no seizure activity on a routine EEG. In these circumstances, there is a two-in-three chance of being able to withdraw seizure medicines. Of course, the other side of this risk is a one-in-three chance of having a seizure within the three years after withdrawing medicine. Some patients find this risk unacceptably high. I advise most patients not to drive for three months during a taper of all seizure medicine.

The clinician should simplify the medication regimen. Complex regimens are not followed by most patients. A drug schedule of one dose per day is more often followed correctly than is a twice, three or four times a day schedule. Monotherapy (one drug) is simpler than polypharmacy (many drugs) and monotherapy avoids drug interactions. About 80% of people with epilepsy can be treated with monotherapy. However, tapering to monotherapy can be difficult, because of transient flare-up of seizures.

Some drugs need to be built up slowly to avoid side effects. Carbamazepine, valproic acid, lamotrigine, primidone, topiramate, tiagabine, vigabatrin all have to be initiated over a period of a few weeks. In contrast, phenytoin, phenobarbital, gabapentin, and levetiracetam can be initiated at a therapeutic dose. Schedules must be written out in advance. Patients should have phone access to the medical team during the dose-titration period to deal with emergence of side effects.

Switching from one medication to another can be difficult. If the second medicine has to be added slowly, then it usually is not advisable to taper the first medication until the second one is at a therapeutic dose. Otherwise, the patient could have seizures while being inadequately protected during the switch. Toxicity is to be expected during the time of medication overlap. Patients need to be warned to expect a temporary period of more side effects and possible withdrawal seizures.

Serum blood levels can be useful guides in treatment of antiepileptic medications, but they are probably over-used. If a patient is doing well without seizures and medi-

cation toxicity, then serum levels may be superfluous. Particularly in cases of polypharmacy, serum levels may help determine which drug is causing toxicity.

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. 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

Brand Name	Generic Name
Ativan	lorazepam
Carbatrol	carbamazepine
Celontin	methsuximide
Cerebyx	fosphenytoin
Depacon	VPA injectable
Depakene	valproic acid
Depakote	divalproex
Depakote-ER	Valproic acid
Diamox	acetazolamide
Diastat	rectal diazepam
Dilantin	phenytoin
Diprivan	propofol
Felbatol	felbamate
Gabitril	tiagabine
Keppra	levetiracetam
Klonopin	clonazepam

Lamictal	lamotrigine
Luminal	phenobarbital
Lyrica	pregabalin
Mebaral	mephobarbital
Mesantoin	mephenytoin
Mysoline	primidone
Neurontin	gabapentin
Peganone	ethotoin
Phenurone	phenacemide
Tegretol	carbamazepine
Tegretol-XR	carbamazepine
Topamax	topiramate
Tranxene	clorazepate
Trileptal	oxcarbazepine
Valium	diazepam
Versed	midazolam
Zarontin	ethosuximide
Zonegran	zonisamide

Medications for partial seizures

The usual medications of first choice for partial seizures are phenytoin or carbamazepine. If one is not effective, then the other is typically tried in monotherapy. If either is not effective, then two-drug therapy can be tried with phenytoin or carbamazepine plus valproic acid, gabapentin, lamotrigine, topiramate, or levetiracetam. Phenobarbital or primidone are also possible add-on medications, or second choices in monotherapy, but again may lead to sedation or depression. Felbamate can be effective as an alternative monotherapy, but has risks for causing aplastic anemia (a very serious blood disorder) or liver injury.

Medications for secondarily generalized seizures

Secondarily generalized seizures respond to the same regimen as do partial seizures.

Medications for absence seizures

The drug of choice for absence (petit mal) seizures is ethosuximide. Mixed absence and tonic-clonic seizures or unresponsive absence seizures are treated with valproic acid as

a second line drug. Because of its potential liver toxicity and expense, valproic acid is not used as the first drug of choice for absence. Lamotrigine, topiramate, zonisamide, benzodiazepines, and possibly levetiracetam are alternative drugs for absence seizures. Phenytoin, carbamazepine, oxcarbazepine, tiagabine, and vigabatrin have no role in the treatment of absence seizures, and occasionally may make them worse. Benzodiazepines can be useful for treatment of generalized seizures, but they are sedating, and the effectiveness tends to wear off over time.

Medications - Primary generalized tonic-clonic seizures

Primarily generalized tonic-clonic seizures are treated with valproic acid as the drug of first choice, particularly if there is a myoclonic component. Phenytoin, carbamazepine, phenobarbital, lamotrigine, topiramate, zonisamide and possibly levetiracetam all can be used for treatment of primary generalized seizures.

**TABLE 5: MEDICATIONS OF CHOICE
(not all FDA-approved for the given indication)**

SEIZURE TYPE	FIRST DRUG	SECOND DRUG
Partial seizures with or without secondary generalization	sei- PHT	CBZ
		GPN
		LEV
		LEV
		LTG
		MSX
		OXC
		PBB
		PRM
		TGB
		TPM
		VPA
Absence seizures	sei- ESM	ZNS
		BDZ
		LTG
		TPM
		VPA
		ZNS
Primary generalized tonic-clonic seizures	VPA LTG	BDZ
		CBZ
		LEV
		PHT
		TPM
		ZNS

Myoclonic seizures	VPA ZNS BDZ	ACZ
		FLB
		LTG
Atonic seizures	sei- VPA BDZ	ZNS
		ACZ
		FLB
		LTG
		TPM
ZNS		

- ACZ = acetazolamide (Diamox)
- BDZ = benzodiazepines (Valium, Ativan, Klonopin, Tranxene, Xanax)
- CBZ = carbamazepine (Tegretol)
- ESM = ethosuximide (Zarontin)
- FLB = felbamate (Felbatol)
- LEV = levetiracetam (Keppra)
- LTG = lamotrigine (Lamictal)
- MSM = methsuximide (Celontin)
- OXC = oxcarbazepine(Trileptal)
- PBB = phenobarbital (Luminal)
- PHT = phenytoin (Dilantin)
- PRM = primidone (Mysoline)
- TGB = tiagabine (Gabitril)
- TPM = topiramate (Topamax)
- VPA = valproic acid (Depakene, Depakote)
- ZNS= zonisamide (Zonegran)

Medications for myoclonic seizures

Myoclonic seizures respond best to valproic acid and to benzodiazepines. Lamotrigine and topiramate can also be of use.

Medications for atonic seizures

Atonic seizures are often poorly responsive and difficult to treat. Valproic acid and benzodiazepines such as clonazepam have been used. Some of the newer drugs, including lamotrigine, vigabatrin and topiramate, may have action against atonic seizures. Felbamate also helps some atonic seizures, but is a potentially very toxic medication.

INDIVIDUAL MEDICATIONS (alphabetical):

Recommendations are solely the opinions of the current author; Not all medications have an FDA indication for the regimen given. The reader with epilepsy should use the “summary information” as a reference source. **Do not change your medication because of information presented here; rather, use it as a starting point for discussion with your physician!**

Dosages are given, except where otherwise specified, as total daily milligrams. For example, Lamictal dose may be listed as “400 mg per day in 2 divided doses,” meaning 200 mg in the morning and 200 mg in the evening. Some drugs can be started more quickly than can others. Dilantin, Neurontin, phenobarbital, Keppra, and benzodiazepines can be initiated rapidly. These drugs therefore go to work quickly against the seizures. Tegretol, Trileptal, Depakote, Lamictal, Topamax, Gabitril, and Zongran must be titrated up in dose over weeks to months, in order to allow the system to adjust and minimize side effects. Such a slow titration is a disadvantage, because it delays the onset of seizure control. The discussion below of individual drugs provides typical initiation schedules for drugs. However, the schedules are general guidelines. A patient who is very sensitive to side effects of medicines, or who already is carrying the burden of several other seizure medicines, might require a slower titration schedule. In contrast, a patient who is having severe seizures might risk a fast initiation schedule in order to control seizures sooner. The treating physician should individualize the initiation schedule. Similar principles apply to the final dosage level, which also must be individualized.

Metabolism (usually liver, kidney, or both) is listed in case you have liver or kidney insufficiency. In that case, dosing might require special adjustment. The cryptic letters and numbers in the metabolism section, such as “CYP 3A4,” specify the specific chemical system responsible for metabolizing the drug. Most readers can ignore this information, but it is useful if a question arises about a possible interaction with a medicine not listed. If that medicine also is metabolized by the same liver system, then there is a higher likelihood of a drug interaction with the seizure medicine. The half-life of a drug measures how long, on the average, it takes to clear half of the drug from the blood. The longer the half-life, the longer the drug sticks around. Drugs with long half-lives, such as phenobarbital or brand-name Dilantin, only need to be taken once a day. Drugs with short half-lives, such as Neurontin, need to be taken 3 or 4 times per day in order to avoid excessive fluctuation of blood levels.

Plasma (or serum) concentrations of anti-epileptic drugs show how much drug is maintained in the blood, and therefore presumably in the brain. The drug levels should ideally be within the therapeutic range. However, these ranges are guidelines, not mandates. If a patient is seizure-free and non-toxic, than checking a drug level will not likely contribute to management. Ranges are averages, and they originally were calibrated for patients on monotherapy. They may not apply to an individual case. Measurement of levels is most useful for phenytoin (Dilantin), whose levels can swing low to high very easily, somewhat useful for carbamazepine (Tegretol), phenobar-

bital, and valproate (Depakote). Levels tend not to be useful for the newer medicines, which have a very broad therapeutic range.

Drug interactions are listed for the generic forms of drug, and are divided into those that affect the seizure medication (increased and decreased effect), and those for which the seizure medication affects another drug. Look up the generic drugs you are on and see if any are in the interaction list. If they are, discuss any problems with your doctor. Not all drug interactions are listed, so when in doubt check with your doctor or pharmacist. Some drugs pairs have more than one type of interaction, causing increased effects in some people and decreased effects in others.

A side effects list cannot be comprehensive, so I have tried to list the most common and the most serious, along with a few others. Do not be paralyzed by the list of side effects! Like the “Ghost of Future Christmas,” it is what might be, not what will be. Some side effects, for example dizziness or fatigue, are so common as to be hard to attribute to a medicine, unless they start and stop with changes in that medicine. The package insert about a drug and the Physician’s Desk Reference (PDR) are required to list all reported side effects of a drug during clinical trials, some of which may be due to other factors than the drug. Many side effects seen in seizure clinics are due to combination toxicity from more than one medicine. Discuss possible side effects of seizure medicines with your medical team.

Benzodiazepines:

The benzodiazepines consist of the “Valium-like” drugs such as Valium itself (diazepam), Klonopin (clonazepam), Ativan (lorazepam), Tranxene (clorazepate), alprazolam (Xanax). 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 syringes without needles, in doses of 2.5, 5, 10, 15, 20 mg. The usual adult dose 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, 15, 22.5 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, lightheadedness, 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, Shire):

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 car-

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),
200 mg (oblong and pink);
- Tegretol-XR
100 mg (round orange pill with a T)
200 mg (round red pill with a T)
400 mg (round brown 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, bupropion, 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 (Zarontin, Pfizer)

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 Zonégren is required. Alternatively, two drugs can be used, such as Zarontin plus Dilantin or Tegretol.

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

Drugs that lower ESM levels: ???

ESM increases effects of: ???

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, Carter-Wallace):

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, Pfizer):

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 mg 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.

Lamotrigine (Lamictal, Glaxo-Smith-Kline):

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 doses 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 increases effects of: ???, 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, UCB Pharma)

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, includ-

ing 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, Pfizer)

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, Novartis)

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 auto-induction 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, numerous companies):

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, doxyrubicin, lamotrigine, oral contraceptives, oxcarbazepine, phenytoin, 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, Pfizer):

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 also can 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 multivitamin, 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)

Liquid for oral: 125 mg/5 ml.

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, diltiazem, 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, Pfizer)

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, Wyeth-Averst)

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 epi-

lepsy. 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, doxorubicin, 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.

Tiagabine (Gabitril, Abbott and Novo-Nordisk):

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 raise TGB levels: ???

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

TGB increases effects of: ???

TGB decreases effects of other drugs: ???

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, Ortho-McNeil):

Topiramate was just released in 1997. It is a sulfa-related drug, like acetazolamide (Diamox) and zonisamide. 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, 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 raise TPM levels: ???

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, Abbott):

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 times 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, erythromycin, 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, non-steroidal anti-inflammatory drugs such as ibuprofen, naproxen, 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 (Sabril, Aventis):

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 neuro-

transmitter. 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 specialized 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.

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, Athena-Elan)

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 known 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 raise ZNS levels: ???

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

ZNS increases effects of: ???

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
- qhs = 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
- os = left eye
- od = right eye

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 compassionate 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 alterna-

tive. 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 (usu-

ally 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.

EPILEPSY SURGERY:

Anti-epileptic drug therapy is effective in approximately two-thirds of people with epilepsy. The rest do not obtain good seizure control or have unacceptable side effects of the medications. The concept of good seizure control is somewhat elusive. How long must a patient go without a seizure before control is considered good? This is a matter of individual differences of opinion. In many 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 every few months is not "too bad." Such a seizure can have a major impact on the quality of life of people with epilepsy. Part of the challenge of epilepsy specialists and pharmaceutical companies is to encourage treating physicians and patients to strive for better control of their seizures, and not just to accept the limitations imposed by occasional seizures.



Candidates for Epilepsy Surgery

Anti-epileptic drug therapy is effective in approximately two-thirds to three-quarters of people with epilepsy. The remainder do not obtain good seizure control or have unacceptable side effects of medication. The concept of good seizure control is somewhat elusive. How long must a patient go without a seizure before control is considered good? This is a matter of individual differences of opinion. In many 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". Such a seizure can have a major impact on the quality of life of people with epilepsy. Part of the challenge of epilepsy specialists and pharmaceutical companies is to encourage treating physicians and patients to strive for better control of their seizures, and not just give up and accept the limitations imposed by occasional seizures.

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 and fear of the high cost of the surgery. This cost can approach \$50,000. Economic analyses taking into account the direct medical costs of uncontrolled seizures indicate that the money can be recovered in 5-10 years after successful seizure surgery. If individuals then can go back to work, lead a more normal life, and start paying their own share of life expenses, then costs are recovered even more quickly. Epilepsy surgery is elective; no person should be pushed into having epilepsy surgery if they do not want it. It may, however, be the best way to eliminate seizures in a particular individual.

The key to epilepsy surgery is localization of the seizure focus. Typically, seizures that can be cured with surgery will arise from one of the inner portions of the temporal lobe, either left or right. Bilateral seizures, in other words those that sometimes start on the left and sometimes start on the right, are not amenable to surgery because removal of both temporal lobes creates very severe memory problems. In terms of seizure surgery, the path of spread of a seizure is not critically important. The surgical target is the seizure focus, the place at which the seizure originates. Secondly generalized tonic-clonic seizures will stop if the focal point of origin is removed.

Most epilepsy surgery is temporal lobe surgery. The approximate area shaded in the prior figure of the brain is the usual target for removal. It is possible to operate on other lobes of the brain and sometimes cure seizures, but the targets and boundaries of surgery are less clear than they are in temporal lobe surgery. An exception to this is surgery in the area

of a lesion. Such lesions may be malformed blood vessels, post-traumatic scars, low grade brain tumors, prior brain abscesses, or developmental lesions such as migration problems, dysplasias, and heterotopias. Surgery around well-circumscribed lesions is often quite successful.

To evaluate a patient for temporal lobe surgery the first key is to make certain that they have epilepsy and not one of the imitators, such as psychogenic (non-epileptic) seizures. EEG may help to localize the focus. The interictal spikes on EEG are suggestive of where seizures come from, but they are not as reliable as the electrical activity at the start of a seizure. For that reason, surgical candidates usually undergo video-EEG monitoring as an inpatient in order to capture five or six of their typical seizures. Medications may be reduced or discontinued while undergoing monitoring, in order to provoke seizures. The hope is to find that all seizures come from some recognizable spot at the anterior to mid portion of one temporal lobe. MRI can be useful to rule out causative lesions and to show a subtle form of scarring in the temporal lobe called mesial temporal sclerosis. This is not always present, but when it is present, it is a strong indication that temporal lobe is involved in the epilepsy.

Positron emission tomography (PET) scan is a relatively new procedure that looks at glucose consumption in the brain. A radioactive tagged glucose analogue is injected into an arm vein. Over the next 30 minutes, the glucose is taken up via the bloodstream into brain cells. A positron isotope decays at every point in the brain where the glucose molecule is taken up. CT techniques can image the distribution of the radioactive glucose. In about 65% of patients with temporal lobe seizure foci, the temporal lobe on the involved side consumes less glucose than its opposite side during the interictal (between seizure) period. If a PET scan happens to be performed fortuitously during a seizure, then the seizure focus consumes much more glucose at that moment in time

Neuropsychological tests are performed to determine whether a patient has impairments in the verbal sphere, usually reflecting injury to the dominant left hemisphere, or in the sphere of picture, face and shape recognition, which usually reflects right hemisphere damage. Neuropsychological testing can screen for depression, which is highly prevalent in this population. Psychosocial adjustment after epilepsy surgery is key to the success of the procedure, since the goal is improvement of quality of life, rather than just attenuation of seizures.

The Wada test is done to localize speech and memory functions in candidates for epilepsy surgery. The internal carotid vascular distribution of half of the brain is put to sleep through injection of a quick-acting barbiturate into

the internal carotid artery (via a catheter placed in the femoral vein at the groin). During the next 5-15 minutes, speech and memory are tested. 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. Global amnesia after injecting one internal carotid artery is a danger signal for surgery, because this result suggests that there may be severe memory problems after the operation.

Some patients appear to be surgical candidates, but the seizure focus cannot be localized precisely. These individuals may undergo invasive monitoring with electrode wires placed into suspect areas of brain, or with sheets of electrodes embedded in plastic (grids or strips) placed over the surface of the brain (Fig. 8). 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 involved brain is done at the same sitting. Only a few percent of patients with epilepsy undergoing surgery will need mapping with a grid.

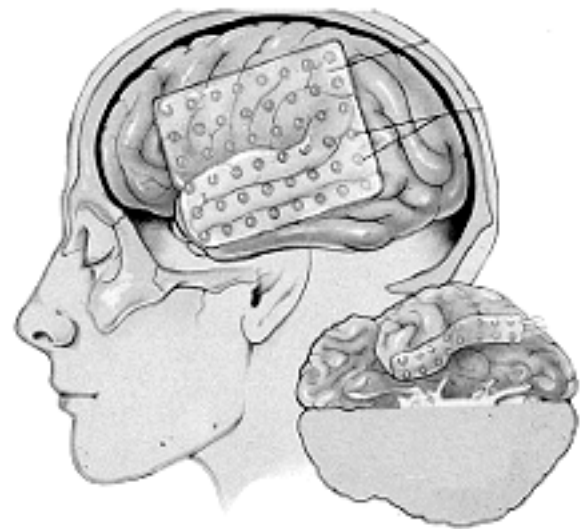


Fig. 8: Grids to map the brain

Upon completion of evaluation to localize the seizure focus (region of seizure onset in the brain), the patient, family, and doctor will discuss whether to proceed with surgery. If so, the patient usually schedules an appointment in clinic to meet the surgeon. Typical duration of hospitalization for a partial temporal lobectomy, the most common procedure, is 4-7 days. The operation is done with the patient under general anesthesia, although a few special instances are done under local anesthesia to allow

further mapping of the brain. If the patient is to have any periods of wakefulness during the surgery, this always will be discussed with the patient in advance.

Temporal Lobectomy Surgical Procedure

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. 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 small coffee cup rim. 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 wires are non-magnetic (MRI compatible), hold the bone firmly in place, and never need to be removed. The membrane over the brain, the dura mater, then is cut open, exposing the temporal lobe. Portions of the temporal lobe are removed by suction, since the brain has a “firm pudding” 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 well less than half the volume of the temporal lobe (Fig. 9)..

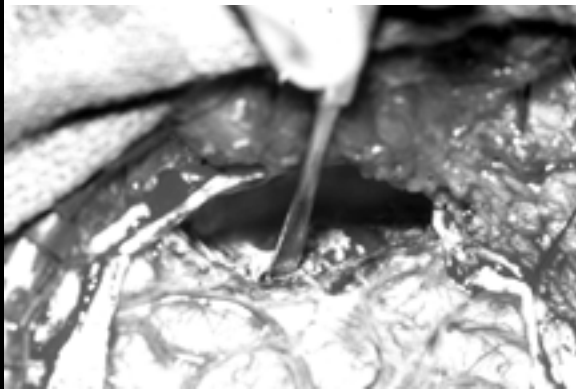


Fig. 9: Portion of brain removed in temporal lobectomy. The patient is lying with right side up, top of the temporal lobe forward. Finger at top gives perspective.

The portion of brain removed never grows back. The space that it occupied fills with the 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. Most delays in returning from surgery are administrative problems

in getting the operation started, so family should not assume that that the surgery is the cause of the long wait. The operation itself usually takes about 2-3 hours.

The family should be prepared for the patient to be disoriented for a day postoperatively. Headache is a clear issue, but over-medication is avoided to allow the patient to wake up. The will be nauseated from the anesthesia, have a sore throat from the breathing tube, and will have swelling and bruising of the forehead and eye on the side of surgery. The swelling increases to a peak 2-4 days after surgery. An overnight or two-day stay in intensive care is common. By day three after surgery, most patients are able to sit in a chair, walk with assistance, and eat. Until post-operative patients can eat and drink, seizure medications are given intravenously. Since not every medicine has an intravenous form, 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:

- Severe speech problems
- Reading difficulties
- Stroke, partial paralysis or numbness
- Personality change
- Deterioration of memory ability
- Partial loss of vision
- Psychiatric deterioration
- Severe depression
- 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 mean that the operation was a failure, 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 is successful about 75% of the time. Patients may be completely cured of their epilepsy and be able to go off all medications, typically about a year after the surgery. Some patients choose to stay on their medications; others become free from seizures, but still require medication. Benefit of surgery may fall short of a complete cure - patients may still have occasional auras (simple partial warnings) or rare breakthrough seizures at times of great stress. Twenty-five percent of the 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 multi-focal.

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. In such instances, people may be able to sit down or protect themselves. 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 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.

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 (atonic 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 Help 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 diges-

tion. 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, heatbeat, 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 stimula-

tor is turned up slowly. Stimulation current ranges from about 0.2 – 4.0 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.

A Few Words on 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 an-

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

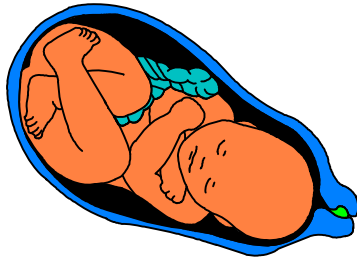
Most people with epilepsy work full and productive jobs. Certain jobs that involve driving, operation of life- or limb-threatening machinery, caustic chemicals, prolonged periods of working on heights or working underwater, should not be done by people with uncontrolled seizures. Any job restrictions should be individualized. The 1990 Americans with Disabilities Act prohibits discrimination in the marketplace against people with disabilities. This includes epilepsy. If people with epilepsy cannot do their job because of seizures, an attempt must be made to make a reasonable accommodation for them within the framework of their employment.

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 are higher risk for women with epilepsy, because of the seizures and the antiepileptic medications. Occasionally, seizures may increase during pregnancy, but they are just as likely to improve or remain stable.



Birth defect risks are a few percent higher in women with epilepsy. The baseline rate of birth defects, large or small, is about 2% for American women. This birth defect risk increases to 5-10% 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 risk factors, but the main birth defect risk is from antiepileptic medications. Monotherapy (one anti-seizure drug, rather than many) is preferred during pregnancy, provided it controls the seizures. Although there is much debate about medications that are best during pregnancy, no scientific study gives us guidance as to one medication truly being safer than another medication.

Phenytoin (Dilantin), and barbiturates can cause cleft lip/palate, or other skull, face, or heart malformations. Valproic acid (Depakote) and carbamazepine (Tegretol, Carbatrol) are linked to open spine problems. Carbamazepine can cause “minor defects”, such as fingernail malformations, or mild facial feature distortions, that resolve by age five. Many other birth defects are possible, and any seizure medicine has the capacity to induce any of the defects. The best rule is to use the single medicine that is most effective in treating the woman’s seizures.

Supplementation with 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 1-5 mg per day. Most over-the-counter daily vitamins contain 0.4 mg (400 micrograms) of folic acid, and most prenatal vitamins, 1 mg. Doses of folic acid of 1 mg or less seem to have no side effects, although high doses can sometimes suppress signs of blood disorders. The folic acid should be taken every day, since most women are not even aware that they are pregnant as the spine is being formed in the first 6 weeks of pregnancy.

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 9 months to the medicine in the placental bloodstream.

A pregnancy registry for women with epilepsy is being maintained in Boston, at 888-233-2334. We recommend that pregnant women with epilepsy call this number, obtain information and provide some information to the registry. By such tracking of pregnancies, we will obtain accurate information on which to base future advice.

Risks of Epilepsy

If you have epilepsy or conditions with faints, blackouts, shaking or confusional episodes, then you should be aware of a few ways in which you should protect your safety.

Driving: Do not drive after a blackout or seizure of a type that might affect your ability to operate a motor vehicle, until you are cleared by the Department of Transportation of your State and your doctor. The State may make exceptions for seizures without blackouts or shaking, seizures only during sleep, seizures with consistent warnings (auras), seizures not likely to occur again. In California, your medical team is required by law to keep the DOT informed of your seizure condition.

Pregnancy: If you may become pregnant, you should discuss the issue of seizures and antiepileptic medications with your medical team. There is no need for alarm, but both seizure medicines and some types of seizures during pregnancy can increase the risk of birth defects. Vitamins with folate can reduce this risk. Do not stop your medications during pregnancy without consulting your physician! Women with epilepsy give birth to normal healthy babies over 90% of the time.

Birth Control Pills: Antiepileptic medications, except for valproic acid (Depakene, Depakote), lamotrigine (Lamictal) and gabapentin (Neurontin), can reduce the effectiveness of low dose birth control pills by causing the liver to clear the hormones rapidly from a woman's system. Unexpected pregnancy can result. Consult your physician for further details.

Injuries from Seizures: Occasionally seizures can provoke injuries. The goal is to live your life as fully as you can, but with common sense about potential injuries. People with infrequent seizures (for example, small seizures less than every three months) may have no need for restrictions. People with frequent seizures should exhibit special care in water, including bathtubs (it may be safer to shower sitting), on prolonged heights (brief climbs up ladders or stairs are usually safe for

most people), around dangerous cutting and chopping machinery without safety guards, or in other obvious potentially dangerous situations. These potential risks apply both to the home environment and to the workplace. Consult your medical team to discuss reasonable safety precautions in your case.

Risks of Antiepileptic Medications: All medicines, including anti-epilepsy medications, have potential risks. The risks of the medicines must be balanced against the risks of seizures and the limit that seizures put on your lifestyle. Medication side effects call for clinical monitoring and sometimes blood tests at intervals to be determined by your physician. You should discuss potential adverse reactions from your medicines with your medical team.

Women with Epilepsy and Small Children: Mothers worry about dropping or otherwise harming their small child during a seizure. This is fortunately a very rare occurrence, but some precautions can be taken. Carry the baby as little as possible. Change the baby on a floor rather than a raised table. Wash the baby in shallow rather than deep water. Enlist help when supervising a small child in dangerous situations such as swimming or climbing.

This general advice does not replace individualized medical advice, which you should obtain from your health care team. There may be other risks that apply to your situation.

For more Information

An excellent source of information is the Epilepsy Foundation (of America), 301-459-3700, 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. 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 numbers.