Applied Therapeutic Drug Monitoring

Volume II: Review and Case Studies

Preface

This second volume presents a continuation of the organized publication of educational material collected by the Therapeutic Drug Monitoring Laboratory Improvement Program, sponsored by the American Assocation for Clinical Chemistry. The purpose of this volume is, like the first, to provide an organized compendium on therapeutic drug monitoring. It is not complete because this field continues to grow. New developments occur weekly.

The Laboratory Improvement Program is a continuously evolving effort. Since publication of Volume I, George F. Johnson, Ph.D., R. Thomas Chamberlain, Ph. D., J.D., and Vijay Aggarwal, Ph.D., have joined the Task Force, replacing us. This turnover keeps the program active, innovative and timely. Mrs. Diane Breunsbach left the program as Director to raise her new family and was replaced by Mr. Don Kaveny. The efforts of both of these individuals have been essential in keeping the program on schedule.

We again wish to acknowledge those laboratorians, researchers, and clinicians throughout North America and Europe who have donated their time to review manuscripts for scientific content. Without their review, this program would have floundered years ago.

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I. Antiepileptic Drugs

1 Seizure Disorders and Epilepsy

W. Edwin Dodson, M.D.

A seizure is an abrupt alteration of brain function due to excessive neural activity in gray matter. The ictus, or sudden attack, can affect mental function and movement. A seizure which causes violent involuntary muscular contraction is a convulsion; a seizure may be convulsive or nonconvulsive. Nonconvulsive seizures, also called absence seizures, are characterized by staring or subtle movements. Although seizures indicate excitatory brain dysfunction, they are nonspecific symptoms which have many causes. A diagnosis of epilepsy is made when seizures recur over time and are not caused by transient metabolic or toxic disorders.

Seizures are relatively common; at least 4% of the population are expected to have seizures sometime during their lives (*1*). The estimated prevalence of epilepsy is 1%. New cases of epilepsy occur in the population at a rate of approximately 0.4/1000 annually. Among new cases of epilepsy, 77% occur in people less than 20 years old. In the United States approximately 2.3 million citizens have epilepsy and 92 652 will develop epilepsy in 1982.

Pathogenesis of Seizure Disorders

The normal cerebral cortex in all higher animals has the intrinsic capacity to manifest seizure discharges (*2*). In experimental animals, normal cerebral cortex develops recurrent paroxysmal discharges when it is surgically isolated from surrounding neural tissue. During a seizure, brain neuronal activity is both qualitatively and quantitatively different from normal. Individual neurons undergo a marked depolarization that is abnormal in both extent and duration.

Different mechanisms appear important in experimental models of absence seizures on the one hand and focal or tonic clonic seizures on the other. In the case of focal and generalized tonic clonic seizures, the seizure activity begins in a localized area of cerebral cortex. The seizure discharge may remain localized or it may spread to involve other areas of brain. If the seizure activity becomes generalized to the entire cortex, it is thought to spread first down to nuclei located in the thalamus and then project back upwards to cortex via the diffusely projecting thalamocortical pathways. Although it was previously thought that generalized seizures began deep in the thalamus or upper brainstem, experimental evidence has not indicated a deep thalamic origin. Thus, it appears that in focal and generalized tonic clonic seizures, the discharge begins in the cortex and secondarily spreads via diffuse brain pathways even when the focal cortical origin is not clinically apparent.

Focal cortical activity can also spread superficially over the cortex to involve contiguous areas. As the seizure discharge spreads to involve larger areas of the cortex, the areas of the body which are involved are progressively enlarged. Consciousness is usually preserved until the discharge involves both cerebral hemispheres simultaneously.

In absence seizures, there appears to be a widespread cortical susceptibility to hypersynchronization by thalamic input. Diffuse synchronous discharges in abnormal cortex can be triggered by what is normally nonepileptogenic stimulation of thalamic nuclei. The spike-and-wave pattern in the surface EEG is associated with alternating discharges of excitatory and inhibitory neurons.

The seizure discharge in brain is associated with marked increases in brain electrical and metabolic activity (*2*). Approximately 50 years ago Hans Berger discovered that abnormal electrical brain rhythms are associated with seizures. The excessive electrical activity of the brain during a seizure can be measured at the scalp with the electroencephalograph. Between the brain and the scalp, electrical potentials are attenuated 58-fold by intervening tissue. Surface potentials must be amplified 1 000 000 times to produce the electroencephalogram (EEG). When a convulsive discharge is localized, it has been estimated that at least 6 cm^2 of cortical surface must be involved to produce a spike of electrical activity on the EEG. When seizure discharges occur only on the inferior surface of the brain, they are undetectable in routine EEG tracings.

At the time of the seizure, the metabolic rate in brain tissue also increases markedly. Within an area of focal seizure discharge, the cerebral metabolic rates for

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glucose and oxygen increase and blood flow increases. These phenomena permit the specific area of brain involved to be visualized. Radiolabeled substrates can be administered and the area of excessive metabolism can be visualized by autoradiography in experimental animals or by positron emission transaxial tomography (PET) scans in patients. Between seizures, in the interictal period, the seizure focus may have a reduced rate of glucose metabolism.

The alterations of behavior and mental function that occur during seizures depend on the location of the seizure discharge in the brain. The discharge may be restricted to a small area of cortex or generalized over both cerebral hemispheres. When the epileptic discharges are localized, patients may have focal movements of parts of the body or perceive sensations or psychic experiences. If the discharge involves the limbic system, patients may have a variety of emotional and cognitive experiences.

Seizures which originate in the temporal lobe are the second most frequent seizure type, following generalized tonic clonic seizures. Partial complex (psychomotor) seizures arising in the temporal lobe are the principal seizure type in an estimated 20 to 44% of patients with epilepsy (*1*). The temporal lobe has widespread effects on mental and motor functioning. Temporal lobe structures, specifically the amygdala and hippocampus, are important components of a network of structures called the limbic system. The limbic system participates in brain functions of emotion, awareness, and memory. Within the temporal lobe, the amygdala is prone to developing seizure discharges. When the amygdala is stimulated over a period of weeks with subconvulsive electrical shocks, the response to the stimulus becomes progressively abnormal, a procedure called *kindling* (*2*). Ultimately, the stimulus, which previously had no effect, elicits a generalized convulsion.

Seizure Types

The international classification of seizure types is the most widely used classification system (Table 1) (*3*). It was developed by a panel of epileptologists, who reviewed videotapes and EEG patterns of patients actually having seizures. The first distinction of the classification system is between localized and generalized seizures. Seizures that begin focally in restricted area of brain and have limited effects are called *partial seizures*. The manifestations of partial seizures may be discrete or simple, or complex when the seizures involve bilateral brain structures and produce unconsciousness.

In partial seizures, the symptoms are referable to the normal function of the involved brain tissue. If the seizure process involves a region of brain which causes

Table 1. International Classification of Seizure Types

I. Partial seizures
   - A. Simple partial (consciousness not impaired)
     1. With motor signs
     2. With somatosensory or special-sensory symptoms
     3. With autonomic signs
     4. With psychic symptoms
   - B. Complex partial (consciousness impaired)
   - C. Partial seizures, secondarily generalized

II. Generalized seizures
   - A. Absence
   - B. Myoclonic
   - C. Clonic
   - D. Tonic
   - E. Tonic clonic
   - F. Atonic

III. Unclassified epileptic seizures (e.g., neonatal)

IV. Addendum

movement, a focal twitching occurs. Partial motor seizures most commonly originate in body areas which have the largest cortical topographic representation, such as the face, the thumb, or the great toe. Seizures can also begin in brain areas which are involved primarily with perceiving tactile sensation. In these circumstances, the patients experience tingling or buzzing in the body part represented by that area of brain. When the seizure causes an elementary movement or sensation, the seizure is said to be a partial seizure with simple symptoms (*simple partial seizure*).

Simple partial seizures produce motor signs, sensory symptoms, autonomic manifestations, and psychic symptoms. Autonomic manifestations include flushing, piloerection, pallor, localized or diffuse sweating. Somatosensory or special sensory symptoms can involve any sensory modality. Special sensory symptoms include hallucinated odors, tastes, visual patterns, or sounds. The sensations are most often vague or amorphous but occasionally are intricate and detailed. The psychic symptoms which occur as a manifestation of partial simple seizures are particularly intriguing. Abnormalities of speech are dysphasic symptoms. Dysmnesic psychic symptoms refer to exaggerated feelings of recognition or familiarity about the environment. A feeling of heightened familiarity is termed *deja vu* (already seen) whereas the feeling of unfamiliarity is termed *jamais vu* (never seen). Seizures can cause a variety of illusions or misperceptions of the environment. The most common are macropsia and micropsia in which objects are perceived as inappropriately large or small, respectively. Psychic symptoms may involve the cognitive processes such as memory; the most common example is forced thinking. During episodes of forced thinking,

the patient recalls a specific event or sequence of events. The recollection is stereotyped from one seizure to the next. Structured or unstructured hallucinations can occur during seizures, although the latter are more common. The most common psychic symptoms caused by partial seizures are affective. Any mood or feeling which is normally experienced can occur; fear is most common. Ecstatic or pleasurable seizures such as those experienced by Dostoevsky are rare (*4*). "...suddenly amid the sadness, spiritual darkness and depression, his brain seemed to catch fire at brief moments, and with an extraordinary momentum his vital forces were strained to the utmost all at once ... all his agitation, all his doubts and worries, seemed composed in a twinkling, culminating in a great calm, full of serene and harmonious joy . . ."

Localized seizure discharges that impair consciousness are termed *complex partial seizures*. Complex partial seizures most often are associated with abnormal discharges in the temporal lobe and often are associated with other manifestations of partial seizures. As noted previously, if the seizure discharge spreads diffusely throughout the cortex, the *partial seizure* evolves into a *secondarily generalized* tonic clonic seizure.

Generalized seizures are characterized by the loss of consciousness, most often with abnormal convulsive movements on both sides of the body. The most common type of convulsion is the *tonic clonic* generalized (*grand mal*) *seizure*, the sole seizure type in approximately 50% of patients with epilepsy (*1*). Tonic clonic seizures, either alone or in combination with other types of seizures, occur in an estimated 85% of patients who have epilepsy. Tonic clonic convulsions are the most dramatic and easily recognized type of seizure. They either occur following secondarily generalization of a partial seizure or appear *de novo* without warning.

An *aura* is a stereotyped sensory or psychic experience which precedes a generalized seizure. Auras in fact are partial seizures. Auras sometimes warn the patient that a generalized seizure is about to occur.

Tonic clonic seizures evolve in a characteristic sequence beginning with the abrupt loss of consciousness and an inarticulate cry. This utterance is created when the patient's diaphragm contracts spasmodically forcing air through the tonically opposed vocal cords. The initial movement culminates in a tonic contraction of body musculature usually lasting 10-20 s. During the period of sustained muscular contraction there is initially a predominance of the flexor muscles followed by the predominance of the extensor muscles causing the patient to first bend then extend. Following the initial tonic contraction, rhythm clonic jerking ensues lasting 3-5 times longer than the tonic phase, ordinarily less than 1 min. The tonic jerking gradually abates into a state of severely reduced muscle tone. During this phase the relaxation of the sphincters may lead to incontinence of urine and feces. The phase of muscular relaxation blends imperceptibly into a period of postictal unresponsiveness from which the patient gradually recovers normal mental functioning, usually in a fragmentary, erratic pattern. In the postictal period, as the patient is awakening, he may be confused and is usually sleepy. Patients who have seizures are consistently amnestic for the time while they were unconscious. However, if the generalized tonic clonic seizure is preceded by a partial seizure, the patient sometimes recalls the sensory or psychic experience which occurred during the prior partial seizure.

Generalized *absence seizures* are characterized by a brief period of staring with loss of contact with the environment (*3*). After absence seizures the recovery of normal consciousness and function is prompt, seemingly immediate. In contrast to generalized tonic clonic seizures, postictal relaxation and sleepiness do not occur. In the most restricted forms, absence seizures are characterized only by interruption of normal behavior with staring. A staring episode due to an absence seizure is often clinically indistinguishable from staring episodes caused by partial complex seizures, but seizure types can be differentiated with the EEG pattern. In an absence seizure, the EEG characteristically indicates the sudden onset of a diffuse bilateral 3/s spike-and-wave pattern. Staring spells caused by partial complex seizures are associated with focal electrical discharge over the temporal lobe. The distinction between absence seizures and partial complex seizures is clinically important because different treatments are required.

Patients with absence seizures often have subtle myoclonic movements involving the eyelids, fingers, arms or shoulders, brief alterations of postural tone, autonomic symptoms or automatisms. Automatisms are stereotyped repetitive complex movements which occur during a seizure, presumably when patterned movements represented in lower brain structures are released from cortical inhibition. Automatisms consist of movements such as chewing, swallowing or fumbling with the clothes. They occur in partial complex seizures, in absence seizures, or sometimes during the recovery period after a generalized tonic clonic seizure.

Clonic seizures, *tonic seizures*, and certain atonic seizures may be regarded as fragments of an abortive generalized tonic clonic seizure. These seizure types are most often seen when patients are treated with antiepileptic drugs which apparently interrupt the orderly convulsive sequence.

Myoclonic seizures are characterized by the diffuse synchronous body jerks and are usually unassociated with the postictal depression. *Atonic seizures* are characterized by a sudden loss of postural tone causing a sudden fall or drop attack if the patient is standing. A mild, brief atonic seizure may cause only a head nod. Atonic and myoclonic seizures usually occur in patients who also have other types of seizures.

Certain types of seizures are not classified by the international classification. Specifically, *neonatal seizures* are not included. The most common seizures in newborn infants are subtle (*5*). Examples of subtle seizures include tonic eye deviation with eye jerking, repetitive fluttering of the eye lids, rowing, swimming or pedaling movements. Infrequently, apnea, the cessation of respiration, is an isolated manifestation of a neonatal seizure. The second most common seizure type in newborn infants is generalized tonic seizures. These are followed in frequency by multifocal clonic seizures and focal clonic seizures. The least common type of neonatal seizure, myoclonic, is characterized by single or multiple flexor jerks of the arms or legs.

Causes of Seizures and Epilepsy

Diseases which affect the brain may cause transient or permanent alterations of brain structure and functioning. The most common transient disorders which cause seizures are metabolic or toxic. Although these transient disorders do not necessarily lead to structural brain damage, brain damage causing later epilepsy can result if the extent and duration of the metabolic derangements are excessive (*6*). Thus, transient metabolic abnormalities that cause acute seizures variably produce permanent brain damage leading to later epilepsy. A classification of seizure disorders is shown in Table 2.

Among the many causes of *nonepileptic seizure disorders*, fever is most common (*7*). In febrile seizures, the transient metabolic abnormality that causes the seizure is fever. Febrile seizures occur in children between the ages of six months and six years. Genetic studies suggest that the propensity to this disorder is inherited. In various studies, from 7.6 to 50% of patients have a positive family history. Although febrile seizures occur in 3.5% of children, only 2% of these children develop epilepsy by age seven. After febrile seizures, the chance of later epilepsy is increased when certain risk factors are present. These include a family history of epilepsy, abnormal development or neurological examination, and a febrile seizure that was focal, prolonged more than 20 min, or recurred within a 24-h period.

Other causes of nonepileptic seizures will be discussed only briefly here. Certain metabolic abnormalities such as hypoxia, ischemia and hypoglycemia are more likely to cause brain damage than others because of their vital role in brain metabolism. Drugs are the most common toxic cause of seizures, usually when doses are excessive. The most common offenders are penicillin, theophylline, tricyclic antidepressants, local anesthetics, phenothiazines, and meperidine. Seizures are common during withdrawal from addiction to barbiturates or alcohol but rare during withdrawal from narcotics.

The term *epileptic seizure disorder* or epilepsy implies that the brain abnormality which causes

Table 2. Classification of Seizure Disorders

I. Nonepileptic (nonrecurrent) seizure disorders
Seizures are prominent or major symptoms of transient brain dysfunction. Later epilepsy may or may not occur.
- A. Neonatal seizures
- B. Febrile seizures
- C. Metabolic disorders
  - Cerebral ischemia
  - Hypoxia
  - Hypoglycemia
  - Divalent cation deficiency (Ca^{++}, Mg^{++})
  - Hyponatremia/hypernatremia
  - Uremia
  - Fever
- D. Toxic disorders
  - Drug abstinence syndromes
  - Drug intoxications
  - Other chemicals
- E. Nutritional deficiency states
- F. CNS infections
- G. CNS neoplasia
- H. Trauma
- I. Cerebrovascular disease

II. Epileptic (recurrent) seizure disorders — epileptic syndromes
Seizures, convulsive or nonconvulsive, recur due to a long-lasting abnormality of brain physiology or structure. An epileptic syndrome may have multiple causes.
- A. Infantile spasms (West syndrome)
- B. Multiple types of seizures with encephalopathy (Lennox-Gastaut syndrome)
- C. Benign Rolandic epilepsy
- D. Petit mal epilepsy
- E. Myoclonic epilepsy
- F. Epilepsy symptomatic of identified brain disease. The epilepsy is characterized by seizure type and cause, for example, posttraumatic epilepsy with generalized tonic clonic seizures.
- G. Epilepsy due to unidentified brain disease (idiopathic, cryptogenic).
  The epilepsy is characterized by typical seizure type, e.g., epilepsy with generalized tonic clonic (grand mal).
- H. Reflex epilepsy
  The epilepsy is characterized by the stimulus which produces seizures.

III. Status epilepticus

recurrent seizures is long lasting, though not necessarily permanent. Whereas the international classification categorizes seizure types, it does not classify the epilepsies; the nomenclature of the epilepsies has never been standardized. The most prevalent diagnostic labels are descriptive. Among patients with seizures, certain groups of patients have clinical features and natural histories that are sufficiently unique to merit syndromic labels. Examples include petit mal epilepsy and infantile spasms. The most useful diagnostic terminology includes the patient's seizure type and etiology, but abbreviated terms abound. For example pyschomotor epilepsy is better labeled as epilepsy with complex partial seizures due to unknown cause.

Infantile spasms are an example of an epileptic syndrome that occurs uniquely in childhood (*8*). Although patients can have several types of seizures, the major seizure type is flexor or extensor spasms. When a cause is identified it is often associated with widespread brain dysfunction. The causes of infantile spasms are identified in approximately 60% of patients and include, in order of decreasing frequency, perinatal asphyxia, tuberous sclerosis, brain malformation, hypoglycemia, hydrocephalus, intraventricular hemorrhage, and certain genetic disorders. Any disease which causes widespread brain damage can cause infantile spasms. As these patients grow older, the infantile spasms abate, but are replaced by other seizure types in at least half of the patients.

In a majority of patients with epilepsy, the cause cannot be identified. Using clinical means, chemical laboratory tests, and the EEG, the cause of seizures can be determined in approximately 25% of older children and adults (*1*). The leading causes of epilepsy are birth injuries, cerebrovascular disease, and head trauma. Among 516 patients in Olmstead County, MN, who developed epilepsy between 1935 and 1967, the cause was identified in 23.3%. In this particular series, birth asphyxia was less prominent than in other series; trauma accounted for 5.2%, vascular disease 5.2%, brain tumor 1%, congenital or genetic disorders 3.9%, infections 2.9% and birth asphyxia 1.4%. Overall, the cause of epilepsy is more easily identified among the very young and old patients.

Since the advent of computerized transaxial tomography (CT brain scanning), approximately one-third of epileptic patients have been found to have brain lesions (*9,10*). Conversely, even with CT scanning no cause for the epilepsy is found in two-thirds of the patients. Among patients with generalized absence epilepsy (petit mal) the incidence of CT abnormalities is very low. Partial motor seizures have the highest probability of being associated with abnormal CT scans, followed by partial complex seizures. The type of abnormality which is found varies with age. Among children with generalized seizures 32% have abnormal CT scan findings, most commonly brain atrophy (*9*).

Among children with partial epilepsy, 43% have CT scan abnormalities whereas with generalized epilepsy only 20% have abnormal CT scans (*9*). Among older patients, atrophic lesions and brain tumors are increasingly common. In one study, brain tumors were found in 37.5% of patients with partial seizures and CT scans were abnormal in nearly 2/3 of adult epileptic patients with partial seizures (*11*). Even among older patients with generalized seizures, only 8.5% had brain tumors.

Brain tumors are a relatively infrequent cause of epilepsy. A brain tumor is more likely to be found when the epilepsy begins in adulthood, particularly after the age of 40 (*12*). Approximately 30% of brain tumors cause seizures although certain types of tumors may cause seizures in more than 50% of cases. The tumors which are most likely to produce seizures grow slowly, gradually encroaching on the cerebral cortex. Brain tumors account for approximately 1-2% of epilepsy in children and in young adults. The incidence of brain tumors causing the onset of epilepsy peaks in the fifth decade. When epilepsy begins after the age of 50, the leading causes are cerebrovascular disease 69%, brain tumors 15.4%, trauma 5.1%, with only 9% of the new cases being undiagnosed.

Epilepsy results from the interaction of multiple factors, one of which is a genetic predisposition. Studies on the inheritance of epilepsy are conflicting (*13*). This is not surprising, because epilepsy is a symptom of brain dysfunction and not a specific disorder. Certain diseases which often cause seizures such as tuberous sclerosis are clearly genetic. In tuberous sclerosis, the inheritance pattern is autosomal dominant and approximately 50% of the patient's offspring will be affected. Metabolic disorders which are associated with seizures such as maple syrup urine disease or phenylketonuria have an autosomal recessive inheritance. When the asymptomatic parents carry the trait, one-fourth of their children manifest the disease. The 3/s generalized spike wave abnormality on the EEG is thought to be inherited as autosomal dominant with an age-dependent expression in the affected offspring. Thirty-five percent of offspring at risk demonstrate the EEG abnormality and 8% have epilepsy. Genetic studies of epilepsy generally indicate that a propensity to develop certain types of seizures can be inherited but other factors are important.

Among patients who undergo surgery to treat intractible seizures the most common causes of seizures are perinatal brain injury (43.3%), followed by infection (26.7%), trauma (16.7%), and brain tumor (5%) (*1*). In 3-5% of surgical specimens the cause of the

seizure cannot be demonstrated pathologically. The most common brain lesion found in these patients is mesial temporal sclerosis. The cause of this lesion is not fully understood, but it may in part be related to previous asphyxia or prolonged seizure activity, plus a special vulnerability of hippocampal brain tissue to metabolic injury.

In *status epilepticus*, seizures are either long lasting or so frequently recurrent as to result in a continuously abnormal mental state (*6,14*). Among various studies the duration of seizures necessary to be defined as status has varied, but 30 min is sufficient, because serious changes in brain metabolism begin to occur after 20 min and progress if the seizure is not stopped. Although any seizure type can occur in status epilepticus, generalized tonic clonic seizures are most common and the most dangerous for the patient.

Status epilepticus with generalized tonic clonic seizures is a medical emergency which requires aggressive, intensive treatment to interrupt the seizures and support the patient's vital functions. Because the chance of permanent brain injury increases as status is prolonged, it should be stopped within 20 min whenever possible. Because the occurrence of status epilepticus often indicates acute brain disease, the cause should be sought aggressively and treated specifically.

Diagnosis and Management of Epilepsies

In the evaluation of patients with seizures, it is important first to document that the abnormal behavior is indeed due to seizures and to obtain a careful description of the ictal experience and behavior. The description of the seizure is used to classify the seizure type and may indicate where the seizure originated in the brain. The physician must first differentiate those patients who have seizures due to transient disorders affecting the brain from those who have recurrent seizures (epilepsy) due to long-lasting alterations of brain physiology or structure (*15,16*).

The initial evaluation includes a careful history and both physical and neurological examinations. Laboratory tests are utilized to rule out infectious, toxic, or metabolic causes of seizures which should be treated specifically when they are present.

The EEG is helpful in characterizing the seizure type and looking for a focal origin of the seizure (*2*). It is particularly valuable if it is obtained fortuitously during a seizure. But this is rare. Usually, the EEG is obtained in the interictal period between seizures. Under these conditions the EEG provides only circumstantial evidence about the origin of the behavior in question. In difficult cases, prolonged EEG recordings or videotapings with EEG may be necessary to determine the nature of a specific recurrent behavior or experience. The finding of an abnormal EEG does not prove that epilepsy is present, nor does the finding of a normal EEG rule out the epilepsy. Among patients with confirmed epilepsy, initial interictal EEG's are normal in 20%, but with repeated interictal recordings the chance of detecting an abnormality increases. Among patients with epilepsy due to focal brain discharges on the inferior brain surface, an EEG abnormality may not be detected at the scalp. If the focus responsible for the seizures is quiescent when the EEG is obtained, it will not be detected.

CT scanning is indicated for those patients who have partial seizures, focal EEG abnormalities, or epilepsy which begins after the age of 20 years. Although middle-aged patients developing epilepsy have the highest probability of brain tumor, brain tumors are found in less than half of this group (*12*). Overall the most common CT scan abnormalities are atrophic lesions with focal or diffuse loss of brain substance (*10*).

Antiepileptic drugs (AEDs) are utilized to prevent seizures in patients with epilepsy (*17*). AEDs are symptomatic therapy which do not treat the underlying cause of seizures. Most of the AEDs are anticonvulsant, that is, they prevent or interrupt seizures. The first chemical to be used as an anticonvulsant was bromide which was introduced by Locock in 1857 (*16*). In 1912, phenobarbital was introduced and in 1937 diphenylhydantoin, later called phenytoin, became available. AEDs are given continuously to prevent the recurrence of seizures.

The selection of the appropriate AED is based upon a careful characterization of the patient's most frequent seizure type (*17*). From a practical point of view, AEDs can be grouped by whether they are effective in treating absence seizures, generalized tonic clonic seizures plus partial seizures, or both of the previous categories (Table 3). AEDs that are effective only against absence seizures are ethosuximide and trimethadione. Anticonvulsants that are effective only against generalized tonic clonic seizures and partial seizures include carbamazepine and phenytoin. Anticonvulsant drugs that are effective against both categories of seizures include valproic acid and certain benzodiazepines. In practice, the physician first determines the patient's seizure type and frequency, considers factors such as potential drug toxicity and unique patient variables such as associated systemic disease and allergic history, and then selects an appropriate AED.

The manner in which the AED is initially administered depends on the urgency of the clinical situation. Status epilepticus is a medical emergency and AEDs must be administered intravenously in high doses to rapidly stop the seizures (*14*). Usually, seizures are

Table 3. The principal AEDs and their clinical spectrum

Drug	Year Introduced	Absence (petit mal)	Partial and generalized tonic clonic
Phenobarbital	1912	±	+
Phenytoin	1938	0	+
Trimethadione	1946	+	0
Primidone	1954	0[a]	+
Methsuximide	1957	0	+
Ethosuximide	1960	+	0
Carbamazepine	1974	0	+
Clonazepam	1975	+	±
Valproic acid	1978	+	+

Primidone is metabolized to phenobarbital.

relatively mild and infrequent, making it preferable to initiate treatment slowly, and avoid early inebriating and sedative side effects to which patients become tolerant as the AED level gradually increases (*15*). In this situation, patients begin taking the medication at a low or average dose and the drug level gradually is increased until a steady state is obtained (*17*). At steady state, the rate of drug intake is equal to the rate of drug elimination and drug levels are relatively constant. To avoid neurological side effects, the physician strives to treat the patient with as little medication as possible. Thus, the dose of AED is gradually increased until either the seizures are stopped or until the patient experiences toxicity.

The effective use of AEDs depends on knowing a patient's seizure type, the selection of an appropriate AED, and the careful follow-up of the patient to evaluate AED efficacy and toxicity (*16*). A knowledge of pharmacokinetics of the AED being given helps the physician use it optimally. The most important pharmacokinetic parameter is the half-life. The half-life of a drug is the amount of time required for one half of the drug to be eliminated from the body. Inter-patient variability in the half-life of AEDs is a major determinant of the different dosage requirements among patients. The half-life is clinically important for several reasons. First, the half-life is directly related to the steady-state concentration, which occurs after chronic dosing. Second, doses should be given at intervals equal to or less than the half-life to avoid excessive fluctuations in drug levels. Third, approximately five half-lives are required for a patient to achieve a steady state after a constant dose is given chronically. Thus, when a physician initiates drug therapy, it is best to wait, whenever possible, until the drug has had time to reach steady state before the patient is reevaluated. Because AEDs have side effects which are additive, it is best to obtain the maximal benefit from an initial AED before adding others. If the initial AED is ineffective, it should be discontinued while a second is tried. The smallest number of AEDs that is sufficient to do the job is preferable. When it is necessary to administer more than one AED, drug concentration measurements are particularly valuable in helping to maximize the effectiveness of each of the AEDs.

AEDs act in the brain to prevent either the spread of seizure activity from the focus or to suppress the abnormal discharges which occur in the focus. When AEDs are given in high doses, the principal toxicities are neurological or neuropsychiatric (*16,17*).

The measurement of AED levels is a valuable clinical adjunct. AED measurements allow a physician to individualize drug doses to produce an appropriate therapeutic concentration for each patient. AED levels should be drawn whenever the physician needs to know them. If a patient has symptoms which might be due to drug toxicity, levels obtained when the symptoms are present are most valuable. If the patient continues to have seizures despite presumably adequate doses, levels are best measured when the AED level is expected to be at its lowest point, usually just prior to taking a dose. Noncompliance in taking AEDs is a prevalent problem. AED levels provide an objective means of assessing compliance and can indicate those patients who need additional encouragement to take their medications regularly.

How effective are AEDs? Although early studies suggested that drug therapy was effective in controlling seizures in most patients, more careful analysis indicate that only 30 to 50% of patients enjoy complete prevention of their seizures for a prolonged period of time (*1*). Certain types of seizures are more easily controlled than others. For example, more than 50% of patients with absence seizures can be controlled with either ethosuximide or valproic acid. When patients are not controlled by one medication alone, an estimated 90 to 95% of patients with absence