Abbreviations

SEIZURE DISORDERS IN ADULTS

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Learning Objectives

1. Evaluate patient information to determine seizure etiology.
2. Distinguish between different seizure types and choose the best pharmacotherapy.
3. Choose appropriate pharmacotherapy for a patient based on his or her attributes and past drug response.
4. Devise a monitoring plan for a given pharmacotherapy.
5. Provide appropriate patient education for a chosen pharmacotherapy.

Introduction

Epilepsy and seizures have been described and treatment has been attempted for at least 4000 years. There are early accounts describing treatment of seizures in ancient Persia, India, and China. Treatments have ranged from drinking a gladiator's blood in first century Rome to the modern era of antiepileptic drugs (AEDs). Potassium bromide was first introduced as treatment for epilepsy in 1857. Phenobarbital and phenytoin followed in the first part of the 20th century. Scientific advances have expanded the AED armamentarium to about 20 drugs that are currently available.

Pharmacist involvement in epilepsy treatment and monitoring exploded in the 1960s with the advent of clinical pharmacy. Therapeutic drug monitoring was recognized as an important component of AED treatment after a 1960 study on a correlation between phenytoin serum concentrations, electroencephalographic findings, and clinical status.

This chapter updates pharmacists regarding the care of patients with epilepsy. A review of the pathophysiology of epilepsy is followed by a discussion of patient care. New developments in pharmacological and surgical approaches to epilepsy treatment are discussed along with a review of recently developed clinical treatment guidelines. Special emphasis is placed on treatment of women with epilepsy. Also addressed are drug monitoring, patient education, and quality improvement.

Pathophysiology

To understand the treatment options available for a patient with epilepsy and to empathize with patient concerns that arise during treatment, pharmacists need a clear understanding of the terms used to describe epileptic conditions and the clinical characteristics of each seizure type. Diagnostic procedures as well as information regarding the epidemiology and prognosis of epilepsy are discussed in this section. Pharmacists may find these data useful in answering questions that patients with epilepsy may ask. Lastly, the therapeutic goals and outcomes are set forth for developing a patient care plan.

Definitions

Terminology to describe seizures and epileptic conditions is fairly standardized. More than one term may be needed to describe a single seizure (e.g., catamenial, complex partial, or drug-resistant epilepsy). Patients also may have more than one seizure type. It is important to know the common terms and definitions for the various seizure types. A seizure is a clinical event that results from an abnormal electrical disturbance in the brain. This electrical activity may produce disturbances in consciousness, motor activity, sensory activity, and/or behavior. On the other hand, a convulsion denotes a seizure that has a motor component, such as involuntary muscle contractions, which can occur in specific muscle groups or be generalized. Epilepsy is a chronic neurological disorder in which patients experience recurrent seizures. The term epilepsy does not refer to one specific seizure type, but is

Abbreviations in this Chapter

AED	Antiepileptic drug
EEG	Electroencephalogram
PRODIGY	Prescribing RatiOnally using Decision support In General practice studY
QOL	Quality of life
SIGN	Scottish Intercollegiate Guidelines Network
SUDEP	Sudden Unexpected Death in Epilepsy
VNS	Vagus nerve stimulation

used generally to describe the condition associated with seizures.

Epilepsy can be further described. Drug-resistant epilepsy is continuation of seizures despite optimal monotherapy with two successive first-line AEDs or with one monotherapy and one combination regimen. Status epilepticus is recurrent seizures without complete recovery of consciousness between attacks or virtually continuous seizure activity for more than 30 minutes, with or without impaired consciousness.

Sudden Unexpected Death in Epilepsy (SUDEP) is the sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence of seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause of death. Catamenial epilepsy is the occurrence of seizures around the time of menses or an increase in seizures in relation to the menstrual cycle.

Seizures are often described by their presumed onset and clinical appearance. Partial seizures arise from one hemisphere of the brain. Partial seizures are sometimes described as focal due to their localized onset. In their most basic form, simple partial seizures, consciousness is not impaired. The patient may experience involuntary twitching or jerking in one extremity, autonomic symptoms (e.g., vomiting or sweating), or altered sensory perceptions (e.g., auditory, visual, olfactory, or gustatory sensations). Complex partial seizures also develop in and are confined to one hemisphere of the brain. However, compared to simple partial seizures, consciousness is impaired. Partial seizures can spread across the corpus callosum to become secondarily generalized seizures.

Generalized seizures involve both hemispheres of the brain at seizure onset. Consciousness is always impaired during a generalized seizure; however, the seizure itself may be extremely brief. The patient experiencing absence seizures may have a blank expression with a sudden interruption of activity. This type of seizure is brief, lasting only a few seconds. Myoclonic seizures are brief, shock-like contractions of the muscles. These jerks usually last only a few seconds, but may be repeated several times in a row. A clonic seizure can be described as a series of bilateral, symmetrical, rhythmic movements. In a tonic seizure, the patient has muscle stiffening and frequently falls to the ground. A tonic-clonic seizure incorporates the stiffening of a tonic seizure in the first phase, then progresses to the bilateral, repetitive movements of the clonic phase. Atonic seizures are characterized by a sudden loss of muscle tone in one or more muscle groups. The patient may slump or fall to the ground, sometimes causing injury.

Etiology

When the cause of a seizure is known and treatable, the disorder is not usually termed epilepsy because the seizures are unlikely to recur. Some of the etiologies for these isolated seizures include electrolyte abnormalities, acute ingestion of alcohol or use of illicit drugs, withdrawal from alcohol or illicit drugs, and prescription drugs. Drugs other than alcohol and dependence-inducing drugs can induce seizures by one of several mechanisms: They can lower the seizure threshold; they can decrease AED serum concentrations by a pharmacokinetic drug interaction; or they can cause another medical condition that may precipitate seizures. Much of the evidence used to support these claims is anecdotal. Some of the drugs that have been implicated in inducing seizures are listed in Table 1-1. Many of these drugs may be necessary to treat other conditions in a patient with epilepsy. In such cases, a risk-benefit assessment is recommended. For example, patients with epilepsy may have comorbid depression. All of the antidepressant drug classes have at least anecdotal reports

Table 1-1. Drugs Reported to Precipitate Seizures

Amphetamines
Anticholinergics
Anticholinesterases
Antidepressants
Antiemetics
Antihistamines
Antipsychotics
Aqueous iodinated contrast agents
Baclofen
β-Blockers
Cephalosporins
Cocaine
Cyclosporine
Estrogen
General anesthetics
Imipenem
Isoniazid
Lidocaine
Lithium
Methotrexate
Methylphenidate
Metronidazole
Narcotic analgesics
Oxytocin
Penicillins
Pyrimethamine
Quinolones
Sympathomimetics
Theophylline
Tramadol

Abbreviations

Table 1-2. Etiologies of Adult Epilepsy

Etiology	Percent of Epilepsy Patients
Idiopathic	68.7
Stroke	13.2
Developmental defects	5.5
Central nervous system trauma	4.1
Central nervous system tumors	3.6
Central nervous system infections	2.6
Degenerative diseases	1.8

of precipitating seizures, but the patient should not be denied treatment based on this evidence. The patient requiring antidepressant drugs should be warned of the potential for increased seizures, and increased monitoring of seizure counts should ensue.

The etiology of epilepsy varies by age group. In adults, about 70% of all epilepsy is idiopathic in origin. Other causes are significantly less represented, as shown in Table 1-2. The choice of AED does not vary based on epilepsy etiology; however, some of the causes of epilepsy will require additional treatment, such as surgical resection of a central nervous system tumor.

Clinical Characteristics

The International Classification of Epileptic Seizures (Table 1-3) was developed by the International League Against Epilepsy in 1969 and revised in 1981 and 1989. This classification system was based on clinical seizure manifestations, electroencephalogram (EEG) patterns during seizures, and EEG patterns between seizures.

About 60% of adults with epilepsy have tonic-clonic seizures (including 20% with secondarily generalized seizures), 20% have complex partial seizures, 12% have mixed tonic, clonic and partial seizures, about 3% have simple partial seizures, and less than 5% have absence seizures, myoclonic seizures, and other seizure types.

The International League Against Epilepsy is currently revising the classification to focus on diagnostic schemes that can be applied to provide a detailed description of an individual patient. The proposal can be summarized as follows: Axis 1 describes the seizure event; Axis 2 is the epileptic seizure type or types; Axis 3 lists any syndromic diagnosis; Axis 4 specifies etiology when this is known; and Axis 5 summarizes the degree of impairment caused by the epileptic condition.

Diagnosis

The diagnosis of epilepsy depends on the results of four evaluations: history and clinical examination, radiological evaluation, laboratory evaluation, and EEG. The purpose of these evaluations is to exclude other disorders in the differential diagnosis. Other disorders that can be commonly mistaken for epilepsy are listed in Table 1-4.

History/Examination

Information regarding the epileptic event should include eyewitness descriptions, if possible, and/or patient impressions of what occurred before, during, and after the event. The history of the event also should screen for any known epilepsy etiologies. Any provoking or ameliorating factors for the event should be noted. A thorough neurological examination should be completed, with additional investigation of any alternative causes of events (e.g., arrhythmias).

Table 1-3. International Classification of Epileptic Seizures

I. Partial Seizures (seizures that begin focally or locally)
  A. Simple partial (no impairment of consciousness)
    1. With motor signs
    2. With somatosensory or special sensory symptoms
    3. With autonomic symptoms
    4. With psychic symptoms (disturbance of higher cerebral function)
  B. Complex partial (impairment of consciousness)
    1. Simple partial onset followed by impairment of consciousness
    2. With impairment of consciousness at onset
  C. Partial seizures that secondarily generalize
II. Generalized
  A. Absence
  B. Myoclonic
  C. Clonic
  D. Tonic
  E. Tonic-clonic
  F. Atonic

Adapted with permission from the American College of Clinical Pharmacy. Welty TE. The pharmacotherapy of epilepsy. In: Mueller B, Bertch K, Dunsworth T, et al, eds. Pharmacotherapy Self-Assessment Program, 4th ed. Neurology Module. Kansas City, MO: American College of Clinical Pharmacy, 2002:46.

Radiological Evaluation

Magnetic resonance imaging studies are the neurological radiological evaluation of choice for the diagnostic workup for epilepsy. Some clinical guidelines in the United Kingdom suggest that neuroimaging is not necessary if the clinician is confident in the diagnosis based on clinical findings and if the patient responds to the first AED used. However, magnetic resonance imaging is particularly important in the following patients: those who develop epilepsy in adulthood; those with a history, examination, or EEG of focal onset; or those whose seizures continue in spite of first-line drugs. In these patients, structural abnormality may be a cause of epilepsy.

Computerized tomography can be used if magnetic resonance imaging is not available or if sudden onset of seizures suggests a neurological emergency such as intracranial bleeding or stroke. However, computerized tomography is much less sensitive or specific than magnetic resonance imaging for routine use in identifying focal epileptogenic lesions.

Laboratory Evaluation

Routine laboratory examination for new-onset seizures should include the following: blood glucose, urea, electrolytes, liver function tests, and serum calcium. If infection or intoxication is suspected, appropriate investigations should be undertaken (e.g., lumbar puncture, complete blood cell counts with differentials, serum alcohol, and serum or urine screen for illicit drugs). An electrocardiogram also should be performed to rule out cardiac causes of events such as syncope.

Table 1-4. Differential Diagnosis for Epilepsy

Vasovagal syncope
Psychogenic non-epileptic events
Anxiety attacks
Cardiac arrhythmias
Hypoglycemia
Transient ischemic attacks
Tics
Migrainous aura

Electroencephalography

Electroencephalography is a cornerstone for the evaluation and diagnosis of a patient in whom epilepsy is suspected. An EEG enables the physician to classify the seizure or epilepsy syndrome and to suggest prognosis. However, the EEG should not be used in isolation to make a diagnosis of epilepsy, because 0.5% of healthy young adults will have incidental epileptiform abnormalities.

Conversely, an EEG alone cannot exclude a diagnosis of epilepsy, because a single, routine EEG shows definite epileptiform abnormalities in only 29–38% of adults who have epilepsy.

Obtaining a series of EEGs demonstrates definite epileptiform abnormalities in 69–77% of those for whom the diagnosis is unclear. Special techniques, such as sleep deprivation, hyperventilation, and photic stimulation EEG recordings or prolonged recordings with video correlates, may be helpful in diagnosing difficult cases.

Epidemiology

In most studies, the overall incidence of epilepsy (excluding febrile convulsions and single seizures) in developed societies has been reported to be around 50 cases/100,000 persons/year (with a range of 40 to 70 cases/100,000 persons/year). In the United States, the incidence of epilepsy ranges from 11 to 103 cases/100,000 persons/year, with the highest incidences occurring during the first year of life and after age 55. The incidences in developing countries are generally higher, in the range of 100 to 190 cases/100,000 persons/year. The reasons for this higher incidence are not entirely clear but may be due to deprivation or infestation. Of interest, recent data suggest that people from socioeconomically deprived backgrounds in developed countries are more likely to develop epilepsy.

Fear of prejudice, lack of reporting, and differences in terminology and analytic methods used in epidemiologic studies contribute to the imprecision in determining the number of individuals with epilepsy. About 8% of the population in the United States will experience at least one seizure during their lifetime. About 2 million people in the United States have epilepsy. The age-adjusted epilepsy prevalence is 6.8 cases/1000 persons and the cumulative incidence through age 74 years is 3.1%.

Table 1-5. Risk Factors for Mortality in Epilepsy

Risk Factor	SMR
Remote symptomatic[a]	2.2–3.3
Congenital neurological deficit	10–25
Generalized tonic-clonic seizures (first 5–10 years after diagnosis)	3.5–3.9
Myoclonic seizures	4.1
Poor seizure control	3.77

[a]Underlying neurological abnormality acquired after birth that provokes seizures.
SMR = standardized mortality ratio.

Prognosis

About 70% of people with epilepsy will become seizure-free with initial appropriate treatment, but 30% will continue to have seizures. The number of seizures in the 6 months after first presentation is the most important predictive factor for remission of seizures. Among those people who have seizures, about one-third have less than one seizure a year, one-third have between one and 12 seizures per year, and one-third have more than one seizure per month.

Life expectancy is shortened for persons diagnosed with epilepsy compared with those who do not have epilepsy. Causes of death in epilepsy may be unrelated to epilepsy (e.g., heart disease or pneumonia), related to the underlying disease (e.g., cerebral tumors or cerebrovascular disease), or epilepsy-related (e.g., suicides, treatment-related, status epilepticus, seizure-associated trauma, or SUDEP). Risk factors for death in epilepsy are listed in Table 1-5. In various case series, the standardized mortality ratio varies considerably. The standardized mortality ratio is defined as the ratio of the observed number of deaths in an epilepsy population to that of the expected number of deaths based on the age- and sex-specific mortality rates in a reference population, in a given time. In large cohort samples, the standardized mortality ratio ranged from 1.6 to 9.3 for patients with epilepsy. Epilepsy etiology appeared to be of paramount importance in the standardized mortality ratio. In one case series, individuals with idiopathic epilepsy had a less than 2-year reduction in life expectancy when diagnosed at age 50 years or older and a less than 1-year reduction when diagnosed before age 30. However, for individuals who had epilepsy secondary to a known cause (e.g., alcohol-related, metabolic disorders, head injury, cerebrovascular accident, or cerebral palsy), life expectancy for women was reduced 11 years and 13 years for men. This cohort study excluded patients with a diagnosed cerebral tumor, a known case which would be expected to shorten life considerably. The emergency situation of status epilepticus carries a significant risk of death. The case-fatality rate for each episode of status epilepticus may be as high as 20%.

Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN). SIGN Publication No. 70, 2003:49.

French JA, Kanner AM, Bautista J, et al; American Academy of Neurology Therapeutics and Technology Assessment Subcommittee; American Academy of Neurology quality Standards Subcommittee; American Epilepsy Society Quality Standards Subcommittee; American Epilepsy Society Therapeutics and Technology Assessment Subcommittee. Efficacy and tolerability of the new antiepileptic drugs, I: treatment of new-onset epilepsy: report of the TTA and QSS subcommittees of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2004;45:401–9.

Abbreviations

Table 1-6. Drugs used for Major Seizure Types

	Partial	Tonic-Clonic	Absence	Atonic	Myoclonic
Drug(s) of choice	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproate	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproate	Ethosuximide Lamotrigine Valproate	Lamotrigine Oxcarbazepine Phenytoin Topiramate Valproate	Lamotrigine Oxcarbazepine Phenytoin Topiramate Valproate
May have therapeutic effect	Clonazepam	Clonazepam	Clonazepam Topiramate	Clonazepam Phenobarbital	Clonazepam
Adjunctive therapy only	Levetiracetam Tiagabine Zonisamide	Levetiracetam Tiagabine Zonisamide	Levetiracetam	Carbamazepine Levetiracetam Tiagabine	Carbamazepine Tiagabine Zonisamide

Sudden Unexpected Death in Epilepsy has emerged as an important cause of mortality in epilepsy, accounting for 2–18% of epilepsy deaths. Most SUDEP cases are unwitnessed; however, reviews of several autopsies have suggested that a seizure occurred either before or at the time of death. Postulated mechanisms of death include cardiac arrhythmia, respiratory arrest, neurogenic pulmonary edema, and asphyxiation. The following risk factors have been associated with SUDEP: frequent generalized tonic-clonic seizures, age 20–50, acquired epilepsy, intractable epilepsy, frequent AED changes, and early-onset epilepsy. Many of these risk factors may be surrogate markers for seizure control, indicating that SUDEP may be most related to seizure frequency or severity. Antiepileptic drugs have been a focus of several studies on SUDEP. Investigators have demonstrated that 50% or more of SUDEP victims had serum concentrations of AEDs below the commonly accepted therapeutic ranges. This finding suggests that drug nonadherence may be associated with SUDEP. One study has shown that patients who had more frequent serum AED concentration determinations were less likely to experience SUDEP. Several investigators have attempted to implicate particular AEDs in SUDEP; however, the number of subjects taking a particular AED has been too small for definite correlations. Until better information is available concerning SUDEP, it is advisable to aggressively treat patients with epilepsy.

Therapeutic Goals/Outcomes

The goals of treating epilepsy are to decrease the frequency of seizures and to prevent psychosocial consequences. Decreasing the seizure frequency will decrease the risks of death, injury to the patient, and injury to others, particularly through motor vehicle accidents. The overall goal number of seizures should always be zero. Many patients with epilepsy find other parts of their lives significantly affected by the seizures they experience. Obvious examples include loss of driving privileges, restrictions on swimming and bathing, and changes in employment. Other, less clear, examples are changes in personal relationships, ability to care for children, decisions about childbearing, and leisure activities. Although a decrease in the number of seizures experienced by individuals leads to an overall improved quality of life (QOL), some psychosocial factors do not improve until seizures are completely controlled.

Quality Patient Care

Provision of high-quality patient care requires the pharmacist to understand pharmacotherapy and nonpharmacological treatments before developing a comprehensive treatment plan for a patient. To assist the pharmacist in these endeavors, guidelines as well as special considerations for women and elderly patients with epilepsy are discussed. Patient education and quality improvement also are emphasized.

Pharmacotherapy

Pharmacotherapy must begin with a plan for initiating therapy. Often patients' seizures are controlled with the first well-chosen therapeutic drug. This section assists the pharmacist in choosing an appropriate initial treatment. For a situation where seizures are incompletely controlled with the initial choice, the pharmacist should use a well-designed strategy for initiating further drugs and refining therapy. These methods are discussed in the following section.

Therapy Initiation

Therapy is usually not initiated after a first seizure for adults. The risk of seizure recurrence is 30–60% after an initial seizure. Guidelines suggest that the following indicators be used to determine whether a first, unprovoked seizure should be treated: the individual has a neurological deficit; the EEG shows unequivocal epileptic activity; the individual considers the risk of having a further seizure unacceptable; or brain imaging shows a structural abnormality. Treatment with an AED is usually initiated after a second seizure, as the risk of further seizures increases to 80–90% after the second seizure. Treatment with an AED reduces the risk of recurrence by 50%.

National Institute for Clinical Excellence. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Clinical Guideline No. 20. London: National Institute for Clinical Excellence, 2004:73.

Abbreviations

Table 1-7. Common Adverse Effects of Antiepileptic Drugs

Antiepileptic Drug	Concentration-related Effects	Idiosyncratic or Less Common Effects
Carbamazepine	Diplopia	Hyponatremia
	Nausea	Leukopenia
	Drowsiness	Aplastic anemia
	Sedation	Rash
Gabapentin	Drowsiness	Weight gain
	Sedation	
Lamotrigine	Insomnia	Rash
	Ataxia	Headache
Levetiracetam	Somnolence	Depression
	Dizziness	Aggression
Oxcarbazepine	Somnolence	Hyponatremia
	Dizziness	Hypersensitivity/ allergy
	Diplopia	
Phenobarbital	Sedation	Cognitive impairment
	Drowsiness	Hyperactivity
	Ataxia	Attention deficit
		Passive-aggressive behavior
Phenytoin	Sedation	Gingival hyperplasia
	Drowsiness	Rash
	Ataxia	Acne
	Nystagmus	Lupus-like syndrome
Tiagabine	Dizziness	Non-convulsive status epilepticus
	Somnolence	
	Irritability	
	Slowed thinking	
Topiramate	Slowed thinking	Renal calculi
	Drowsiness	Weight loss
	Ataxia	Glaucoma
	Dizziness	Paresthesia
Valproate	Tremor	Hepatotoxicity
	Drowsiness	Weight gain
	Sedation	Pancreatitis
	Nausea	Hyperammonemia Encephalopathy
Zonisamide	Somnolence	Renal calculi
	Dizziness	Paresthesia
		Weight loss
		Rash
		Psychosis

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Table 1-8. Antiepileptic Drug Interactions

Initial Drug	Added Drug	Effect of Added Drug on Initial Drug
Carbamazepine	Phenobarbital	↓ concentration
	Phenytoin	Variable
	Felbamate	↑ metabolite concentration
Phenytoin	Carbamazepine	Variable
	Valproate	↑ concentration
	Felbamate	↑ concentration
	Topiramate	↑ concentration
	Oxcarbazepine	↑ concentration
Phenobarbital	Phenytoin	Variable
	Carbamazepine	↓ concentration
	Valproate	↑ concentration
Valproate	Phenytoin	↓ concentration
	Phenobarbital	↓ concentration
	Carbamazepine	↓ concentration
	Topiramate	↓ concentration
Lamotrigine	Phenytoin	↓ concentration
	Carbamazepine	↓ concentration
	Valproate	↑ concentration
Topiramate	Carbamazepine	↓ concentration
	Phenytoin	↓ concentration
	Valproate	↓ concentration
Tiagabine	Carbamazepine	↓ concentration
	Phenytoin	↓ concentration
	Phenobarbital	↓ concentration
	Valproate	↓ protein binding
Oxcarbazepine	Carbamazepine	↓ concentration
	Phenytoin	↓ concentration
	Phenobarbital	↓ concentration

Reprinted with permission from the American College of Clinical Pharmacy. Welty TE. The pharmacotherapy of epilepsy. In: Mueller B, Bertch K, Dunsworth T, et al, eds. Pharmacotherapy Self-Assessment Program, 4th ed. Neurology Module. Kansas City, MO: American College of Clinical Pharmacy, 2002:51.

Patients should be treated with a single AED wherever possible. Patient compliance is improved, adverse effects are easier to manage, and fewer drug interactions occur with monotherapy than with polytherapy. The first AED should be chosen based on the presumed seizure type for that patient (Table 1-6). Other considerations such as potential adverse effects, teratogenic effects, interactions with concomitant drugs, effect on concomitant disorders, or cost also may help determine the choice of AED (Tables 1-7, 1-8, and 1-9). All AEDs have similar efficacy in newly diagnosed epilepsy, provided a first-line AED is chosen. Between 70% and 80% of individuals are successfully treated with one of the available AEDs. Because AEDs may cause adverse central nervous system effects during initial use, doses as low as 33%–25% of the typical maintenance dose may be selected, and doses may be gradually increased over the next few weeks. Specific details of dosing increases can be found in the product manufacturer's literature or any standard reference text. Exceptions are made for individuals who need loading doses of AEDs to control potentially life-threatening seizures, such as patients who have experienced status epilepticus.

Pharmacotherapy Refinements

Failure to control seizures completely with the first well-tolerated AED is a predictor of drug-resistant epilepsy. Failure to respond well to AEDs may be due to incorrect diagnosis of epilepsy, inappropriate choice of AED for the epilepsy type, failure to take the prescribed AED, an underlying cerebral neoplasm, or drug or alcohol abuse. Each of these potential causes should be explored before

French JA, Kanner AM, Bautista J, et al; American Academy of Neurology Therapeutics and Technology Assessment Subcommittee; American Academy of Neurology quality Standards Subcommittee; American Epilepsy Society Quality Standards Subcommittee; American Epilepsy Society Therapeutics and Technology Assessment Subcommittee. Efficacy and tolerability of the new antiepileptic drugs, II: treatment of refractory epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2004;45:410–23.

Abbreviations

Table 1-9. Adult FDA Indications, Non-epileptic Uses, Pregnancy Categories, and Dosage Forms for Antiepileptic Drugs

Drug	FDA-Approved Adult Epilepsy Indication(s)	Non-epileptic Uses	Pregnancy Category	Dosage Forms
Carbamazepine	1. Partial seizures with complex symptomatology 2. Generalized tonic-clonic seizures 3. Mixed seizure patterns	Trigeminal neuralgia Neuropathic pain Bipolar disorder	D	Tablets 200 mg Chewable tablets 100 mg Extended-release tablets 100 mg, 200 mg, and 400 mg Extended-release capsules 200 mg and 300 mg Suspension 100 mg/5 ml
Clonazepam	1. Akinetic seizures 2. Myoclonic seizures 3. Absence seizures	Anxiety	D	Tablets 0.5 mg, 1 mg, and 2 mg
Ethosuximide	Absence epilepsy	None	C	Capsules 250 mg Suspension 250 mg/5 ml
Felbamate	Monotherapy or adjunctive therapy for partial seizures with and without generalization with appropriate risk-benefit assessment	None	C	Tablets 400 mg and 600 mg Suspension 600 mg/5 ml
Fosphenytoin	1. Control of generalized, convulsive status epilepticus 2. Prevention and treatment of seizures occurring during neurosurgery 3. Short-term substitute for oral phenytoin	None	D	Injection 50 phenytoin equivalent/ml
Gabapentin	Adjunctive therapy for partial seizures with or without secondary generalization	Neuropathic pain Migraine prophylaxis Essential tremor Bipolar disorder	C	Capsules 100 mg, 300 mg, and 400 mg Tablets 600 mg and 800 mg Suspension 250 mg/5 ml
Lamotrigine	1. Adjunctive therapy for partial seizures 2. Conversion to monotherapy for partial seizures in those receiving therapy with a single enzyme-inducing AED	Trigeminal neuralgia Bipolar disorder	C	Tablets 25 mg, 100 mg, 150 mg, and 200 mg Chewable/dispersible tablets 2 mg, 5 mg, and 25 mg
Levetiracetam	Adjunctive therapy for partial onset seizures	None	C	Tablets 250 mg, 500 mg, and 750 mg Solution 100 mg/5 ml
Oxcarbazepine	Monotherapy or adjunctive therapy for partial seizures	Bipolar disorder	C	Tablets 150 mg, 300 mg, and 600 mg Suspension 300 mg/5 ml
Phenobarbital	1. Generalized seizures 2. Partial seizures	Insomnia	D	Tablets 8–100 mg Elixir 20 mg/5 ml Injection 30–120 mg/ml
Phenytoin	1. Generalized tonic-clonic seizures 2. Complex partial seizures	Trigeminal neuralgia	D	Capsules 30 mg, 100 mg, 200 mg, and 300 mg Chewable tablets 50 mg Suspension 125 mg/5 ml Injection 50 mg/ml
Tiagabine	Adjunctive therapy for partial seizures	None	C	Tablets 2 mg, 4 mg, 12 mg, 16 mg, and 20 mg
Topiramate	1. Adjunctive therapy for partial onset seizures 2. Adjunctive therapy for primary generalized tonic-clonic seizures	Neuropathic pain Migraine prophylaxis Essential tremor Bipolar disorder	C	Tablets 25 mg, 50 mg, 100 mg, and 200 mg Sprinkle capsules 15 mg and 25 mg
Valproate	1. Monotherapy and adjunctive therapy for complex partial seizures 2. Monotherapy and adjunctive therapy for simple and complex absence seizures	Trigeminal neuralgia Migraine prophylaxis Bipolar disorder	D	Capsules (valproate) 250 mg Sprinkle capsules (divalproex sodium) 125 mg Tablets (divalproex sodium) 125 mg, 250 mg, and 500 mg Extended-release tablets (divalproex sodium) 250 mg and 500 mg Syrup (valproate) 250 mg/5 ml Injection (valproate) 100 mg/ml
Zonisamide	Adjunctive therapy for partial seizures	None	C	Capsules 25 mg, 50 mg, and 100 mg

Pregnancy category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Pregnancy category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
FDA = Food and Drug Administration.

declaring an AED a therapeutic failure. If the initial treatment is unsuccessful, monotherapy using a second drug should be attempted. In general, the second drug is initiated at a low dose and increased slowly. When a reasonable therapeutic dose is achieved, the first drug is slowly tapered and discontinued. Because seizures are more likely when an AED change is in progress, the patient should practice extra caution during the changeover period. A potential difficulty is encountered if seizures cease when the second AED is titrated to the full dose, but before the first drug is tapered. Many patients and health care providers are reluctant to then discontinue the first drug, in case the combination of AEDs is most helpful. In this scenario, it is most likely that the second drug alone resulted in the decrease in seizure frequency, and discontinuation of the first drug should be encouraged.

When two AEDs have failed as monotherapy, the chance of seizure freedom with further monotherapy is low. Overall, 20–30% of patients have intractable or uncontrolled seizures or have significant adverse effects secondary to drugs, which limit the use of AEDs. Rational polypharmacy (also called combination, adjunctive, or add-on therapy) can be considered when treatment with two first-line AEDs has failed or when the first well-tolerated drug substantially improves seizure control but fails to produce seizure-freedom at maximal dosage. Various authors have suggested that AEDs with different mechanisms of action be chosen, but evidence of the effectiveness of this strategy is lacking. If the patient continues to experience seizures after therapeutic trials of two AEDs as monotherapy or one AED as monotherapy and another rational polytherapy regimen, referral for assessment for neurosurgical treatment should be considered.

Common Severe Adverse Effects/Interactions/Therapeutic Contraindications

The common and severe adverse effects and interactions of AEDs are given in Tables 1-7 and 1-8. One United States study examined patients' concerns regarding their current AED and found that patients' concerns, listed in order of importance to the patient, were overall energy level, school performance, concern about having children, overall QOL, ability to remember things, ability to concentrate, ability to think clearly, emotional and mental well-being, coordination and balance, inability to drive, impaired sex life, and job performance. Unfortunately, many currently available AEDs adversely affect these concerns. Some of these adverse effects may be alleviated by dose reduction. Many patients, however, must balance the risk of having some adverse effects with the benefits of improved or complete seizure control.

Many AEDs affect hepatic enzymes, particularly the cytochrome P450 enzyme systems that are metabolic pathways for some AEDs (Table 1-10). Enzyme induction can result in drug interactions among AEDs when they are used concurrently. Such interactions may lower AED serum concentrations and cause loss of seizure control. Carbamazepine is a self-inducing AED whereas phenytoin appears to be a self-inhibitor of its own metabolism. With the exception of phenytoin and valproic acid, AEDs have linear elimination pharmacokinetics (i.e., progressive increases in drug doses produce proportional increases in serum concentrations). Phenytoin has nonlinear pharmacokinetics, even in the normal therapeutic range, and valproic acid has nonlinear protein binding at high serum concentrations (Table 1-11).

Table 1-10. The Interaction of Hepatic Enzymes and Antiepileptic Drugs

Enzyme	Substrate	Inducer	Inhibitor
CYP1A2	Carbamazepine		
CYP2C8	Carbamazepine		
CYP2C9	Phenobarbital Phenytoin Valproate Carbamazepine	Carbamazepine Phenobarbital Phenytoin	Valproate
CYP2C19	Phenobarbital Phenytoin Valproate	Phenytoin Phenobarbital	Felbamate Topiramate
CYP2D6	Zonisamide		
CYP3A4	Carbamazepine Tiagabine Zonisamide	Carbamazepine Phenobarbital Phenytoin Felbamate	
Uridine diphosphate glucuronyl-transferase	Lamotrigine Carbamazepine	Lamotrigine Phenobarbital Phenytoin	Valproate

CYP = cytochrome P450.
Reprinted with permission from the American College of Clinical Pharmacy. Welty TE. The pharmacotherapy of epilepsy. In: Mueller B, Bertch K, Dunsworth T, et al, eds. Pharmacotherapy Self-Assessment Program, 4th ed. Neurology Module. Kansas City, MO: American College of Clinical Pharmacy, 2002:51.

Nonpharmacological Therapy

The vast majority of patients with epilepsy are treated with drugs. As previously discussed, the likelihood of becoming seizure-free by changing or adding drugs declines precipitously after failure of two AEDs. It is at this point when patients are declared drug-resistant that a surgical evaluation is often proposed. Although drug-resistant epilepsy is defined as failure of two AEDs at optimized doses or one AED as monotherapy and another rational polytherapy regimen, a number of patients have tried many more AEDs, alone or in combination, before surgery is considered. The two surgical methods used are resection and vagus nerve stimulation (VNS).

Resection

Extensive presurgical evaluation is performed to determine if a region of cerebral cortex can be isolated as the epileptogenic zone and if this area could be removed or disconnected with a low risk of neurological or cognitive disability. Typical evaluative procedures are given in Table 1-12. If a definite epileptogenic zone is identified, it can be removed by a variety of resection techniques, often with excellent clinical results. In one large series of temporal lobe resections, 67.9% of patients were seizure-free at 1 year, 24% had significant improvement,

Abbreviations

Table 1-11. Dosing, Therapeutic Serum Concentrations, and Pharmacokinetic Parameters for Common Antiepileptic Drugs

Drug	Initial Dose	Usual Maintenance Dose	Therapeutic Serum Concentration (mcg/ml)	Bioavailability (%)	Plasma Protein Binding (%)	Volume of Distribution (L/kg)	Eliminated Unchanged (%)	Clinically Active Metabolite	Half-Life (hours)
Carbamazepine	200 mg PO BID	800–1200 mg/day divided BID (sustained release) or TID-QID (standard release)	4–12	> 70	40–90	0.8–1.9	Little, if any	10, 11-epoxide	12–17, after autoinduction
Clonazepam	0.5 mg PO TID	Maximum 20 mg/day divided TID	20–80 ng/ml	100	47–80	3.2	Little	7-amino	30–40
Ethosuximide	250 mg PO BID	500–1000 mg/day divided BID	40–100	100	0	0.6–0.7	10–20	None	60
Felbamate	1200 mg/day PO divided TID-QID	1200–3600 mg/day divided TID-QID	Not established	> 90	22–36	0.74–0.85	40–50	None	12–20
Gabapentin	300 mg PO TID	900–3600 mg/day divided TID-QID	Not established	Dose dependent	< 3	0.65–1.04	75–80	None	5–9
Lamotrigine	50 mg PO QD (with enzyme inducers) 25 mg PO QOD (with valproate)	150–500 mg/day divided BID-TID	Not established	98	55	0.9–1.2	10	None	24 (monotherapy) 12–15 (with inducers) 70 (with valproate)
Levetiracetam	500 mg PO BID	1000–3000 mg/day divided BID	Not established	100	< 10	Unknown	66	None	6–8
Oxcarbazepine	300 mg PO BID	1200 mg/day divided BID	Not established	100	67	0.7	< 1	10-mono-hydroxy	2 (oxcarbazepine) 9 (MHD)
Phenobarbital	0.25–0.5/ mg/kg/day PO divided BID-TID	1–3 mg/kg/day divided BID-TID	15–40	80–100	40–60	0.7–1	25	None	49–120
Phenytoin	100 mg PO TID	5–7 mg/kg/day divided QD-TID	10–20	85–95	> 90	0.6–0.8	< 5	None	20[a]
Tiagabine	4 mg PO QD	32–56 mg/day divided QID	Not established	90–95	96	1.4	2	None	7–9 (monotherapy) 2.5–4.5 (with inducers)
Topiramate	25–50 mg PO QD	100–400 mg/day divided BID	Not established	80	13–17	0.6–0.8	70	None	21 (monotherapy) 11–16 (with inducers)
Valproate	10–15 mg/kg/day PO divided QD (extended release) BID-QID (delayed and standard release)	30–50 mg/kg/day divided QD (extended release) BID-QID (delayed and standard release)	40–100 (150)[b]	100	> 90	0.2	< 5	Unknown	8–15
Zonisamide	100 mg PO QD	100–600 mg/day divided QD-BID	Not established	Unknown	40	1.45	35	None	63

[a]Because of Michaelis Menton pharmacokinetics, half-life increases with increases in serum concentration.
[b]The upper end of the valproate serum concentration range is not definitely established; some laboratories report as 100 mcg/ml and others as 150 mcg/ml.
BID = 2 times/day; MHD = 10-monohydroxy metabolite; PO = orally; QD = daily; QID = 4 times/day; QOD = every other day; TID = 3 times/day.

and only 8.1% showed no improvement. If the zone is quite large, removal of the entire hemisphere (i.e., hemispherectomy) has been successful. Alternatively, an attempt to "disconnect" the epileptogenic zone from other areas of the brain can be made when removal is deemed to be associated with significant neurologic or cognitive impairment. Procedures may include a corpus callosotomy where the corpus callosum is either partially or completely sectioned, or a multiple subpial transection in which the horizontal connections within a cortex are severed.

Vagus Nerve Stimulation

Although the effect of VNS on central nervous system activity has long been recognized, the first approval of a VNS device by the Food and Drug Administration occurred in 1997. The VNS system consists of an electrical lead that is attached to the vagus nerve in the neck and a pulse generator that is implanted in the pectoral muscle. The device emits an approximate 30-second current at a set interval (0.5–180 minutes). The amount and frequency of stimulation can be adjusted by an external programmer at the health care provider's office. The patient also is given a magnet that can be used either to initiate stimulation if he or she experiences a seizure prodrome or to temporarily interrupt stimulation.

The precise mechanism of the VNS antiepileptic effect is unknown, but it may involve upregulation of inhibitory neurotransmitters and changes in cerebral blood flow. Although most patients who receive VNS do not become seizure-free, many have substantial reductions in their seizures. In clinical studies, between 14% and 50% of subjects had at least a 50% reduction in seizure number.

The VNS device is Food and Drug Administration-approved for marketing as an adjunctive therapy in adults and adolescents older than 12 years with refractory partial onset seizures. In the European Union, the device is indicated for partial or generalized onset seizures. Practical criteria for VNS use include medically refractory seizures, adequate trials of at least two or three AEDs, exclusion of non-epileptic events (such as psychogenic events and syncopy), and ineligibility for other epilepsy surgery. Assessment as to suitability for a potentially curative resective procedure should be made before considering palliative procedures such as VNS.

Adverse effects of VNS involve surgical complications (such as infection) and temporary vocal cord paralysis, which are relatively rare (1–2% of patients). Common adverse effects usually occur during the electrical pulse delivery and include voice alteration (50%), increased coughing (41%), paresthesia (27%), dyspnea (18%), and dyspepsia (12%).

Treatment Plan

Therapeutic end points are established for epilepsy, and several organizations have developed guidelines for attaining these end points. The following section evaluates the guidelines that are in place for epilepsy. Although guidelines are an excellent starting point, patient characteristics must be considered to develop an individualized treatment plan for a patient. Two groups of patients with special needs, women and the elderly, are addressed in this section. When a patient begins treatment for epilepsy, medications must be monitored. The role of therapeutic drug monitoring and special situations regarding bone effects, hypersensitivity, and adherence with AEDs are presented in this section. As with all disease states, the pharmacist should document his or her activities in patient care. Some practical methods of documentation are addressed in this section.

Table 1-12. Presurgical Evaluations

- Clinical history (including AEDs tried and serum concentrations obtained)
- Ictal and interictal electroencephalography (may also include video correlations of EEG, semi-invasive electrode placement, and invasive electrode placement)
- Neuroimaging (MRI, single photon emission computer tomography, positron emission tomography, computer tomography, magnetic resonance spectroscopy)
- Neuropsychological assessment (neuropsychological testing, amobarbital sodium language and memory testing, and psychosocial evaluation)

AED = antiepileptic drug; EEG = electroencephalogram; MRI = magnetic resonance imaging.

Therapeutic End Points

Outcome measures have been suggested by the Scottish Intercollegiate Guidelines Network (SIGN): seizure frequency, seizure severity scales, assessment of the interictal state adverse events, neuropsychological assessment, and QOL.

In general, the AED dose should be slowly advanced until the seizures stop or intolerable toxicities develop. It is helpful to share this plan with the patient and seek his/her agreement to such increases of the drug. The issue of duration of therapy is slightly more difficult. Once a therapeutic dosage is obtained and the patient is tolerating it well, the dose is maintained until the patient has additional seizures, is seizure free, or until the patient remains at the maintenance dose for up to 5–10 times the average seizure interval at baseline. For example, if a patient has seizures twice a week, a trial of 3–5 weeks would be adequate to assess seizure frequency at that dose. If the patient has a seizure during that time and the drug is at a steady-state concentration (assessed by allowing 3–5 half-lives from the last dose change or by two constant serum concentrations), the dose should be increased to the next level and the efficacy and adverse effects reassessed.

Benbadis S, Chelune GJ, Stanford LD, Vale FL. Outcome and complications of epilepsy surgery. In: Wyllie E, ed. The Treatment of Epilepsy: Principles and Practice, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1197–1214.

Wheless JW. Vagus nerve stimulation. In: Wyllie E, ed. The Treatment of Epilepsy: Principles and Practice, 3rd ed. Philadelpia: Lippincott Williams & Wilkins, 2001:1007–18.

Abbreviations

Table 1-13. Summary of Treatment Guidelines for Epilepsy

Agency	Topics	Multi-Disciplinary Input	Year Published	Scheduled Review	World Wide Web Availability
Agency for Healthcare Research and Quality	Newly diagnosed epilepsy	Yes	2001	None	*www.ahrq.gov/clinic/epcix.htm*
	Treatment-resistant epilepsy	No	2003	None	*www.ahrq.gov/clinic/epcix.htm*
American Academy of Neurology	Efficacy and tolerability of the new antiepileptic drugs I and II	Yes	2004	None	*www.aan.com*
	Management issues for women with epilepsy	No	1998	None	*www.aan.com*
	A guideline for discontinuing antiepileptic drugs in seizure-free patients	No	1999	None	Not available on Web
Scottish Intercollegiate Guidelines Network	Diagnosis and management of epilepsy in adults	Yes	2004	As needed	*www.sign.ac.uk*
National Institute for Clinical Excellence	Epilepsy: the diagnosis and management of epilepsy in children and adults	Yes	2004	Every 4–6 years	*www.nice.org.uk*
Prescribing RatiOnally using Decision support In General practice studY	Drug-focused epilepsy treatment	Yes	2004	Every 3 years	*www.prodigy.nhs.uk*

Guidelines and Algorithm

Several epilepsy guidelines are available that outline either an overall treatment strategy for patients with epilepsy or a focus on a specific issue. Many current treatment guidelines are not from expert bodies in the United States; therefore, some consideration is necessary regarding common medical practice in the countries of guideline origin. These guidelines are summarized in Table 1-13. Figure 1-1 presents a possible algorithm for approaching treatment in an individual with epilepsy. Three important guidelines include SIGN, National Institute for Clinical Excellence, and Prescribing RatiOnally using Decision support In General practice studY (PRODIGY), each of which is discussed below. In addition, the Agency for Healthcare Research and Quality has published a systematic review with recommendations for treatment, and the American Academy of Neurology has developed Practice Parameters, also discussed below.

Scottish Intercollegiate Guidelines Network

In April 2003, SIGN published a national clinical guideline for Scotland titled Diagnosis and Management of Epilepsy in Adults. This guideline covers diagnosis and treatment in a somewhat perfunctory fashion. Women's issues including contraception, pregnancy, and hormone replacement therapy are addressed clearly. A section describing models of care and audit criteria for epilepsy treatment is included; however, the models provided in SIGN are not broadly applicable to the United States health care system. The impact of the SIGN guideline has been evaluated systematically. General practitioners in one area of Scotland were randomized to one of three methods of education on the guidelines: control intervention (received mailed SIGN guideline), intermediate intervention (control intervention, plus participated in workshops regarding the guideline and received structured protocols), and intensive intervention (intermediate intervention plus a nurse specialist who supported and educated practices). There was no difference among the three practitioner groups, based on their patients' outcomes measures of general or epilepsy-specific QOL. The authors also reported poor attendance at the workshops and poor use of the nurse specialist, which may have obscured potential differences in this intent-to-treat design. The authors and others have speculated that the general practitioners may not have had enough time and resources to implement changes in practice or may not have perceived a need for a change in practice.

National Institute for Clinical Excellence

Epilepsy: The Diagnosis and Management of Epilepsy in Children and Adults, the guideline from the National Institute for Clinical Excellence in the United Kingdom, was released in late October 2004. This evidence-based guideline emphasizes the need to include the patient in decision-making and specifies the types of information that should be provided to patients and families. These specifics may be especially helpful to health care providers developing epilepsy-centered practices.

A significant amount of information on treatment of special populations with epilepsy is included. Populations discussed include women, people with learning disabilities, pediatrics, elderly, and racial and ethnic groups with epilepsy. A guidance, Newer Drugs for Epilepsy in Adults was issued in March 2004, in which guidelines for prescribing newer AEDs are given.

Davis J, Roberts R, Davidson DL, et al. Implementation strategies for a Scottish national epilepsy guideline in primary care: results of the Tayside Implementation of Guidelines in Epilepsy Randomized (TIGER) trial. Epilepsia 2004;45:28–34.

Abbreviations

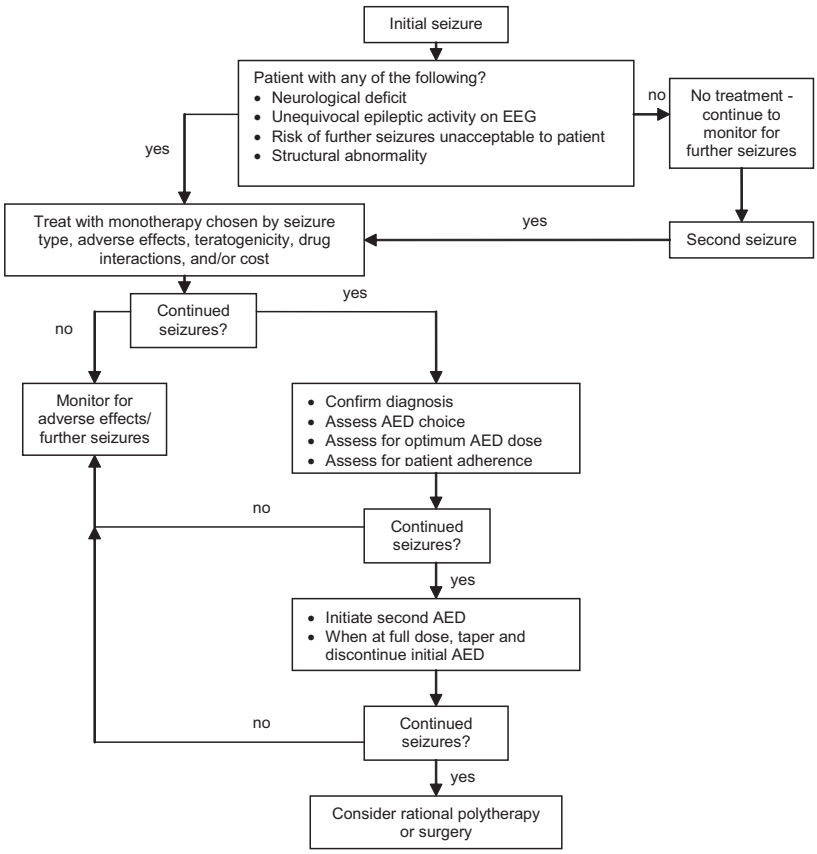

Figure 1-1. Treatment of epilepsy.
AED = antiepileptic drug; EEG = electroencephalogram.

Prescribing RatiOnally using Decision support In General practice studY

The PRODIGY guidances were developed by a multidisciplinary team based at the Sowerby Centre for Health Informatics in Newcastle, England. The guidance for epilepsy is based on the SIGN and National Institute for Clinical Excellence guidelines. The information is provided in an easy to read question-and-answer format. Aimed at general practitioners, this guidance emphasizes differential diagnoses, prognosis, and management issues.

The PRODIGY guidances provide patient information leaflets that may be useful for educational sessions. Specific scenarios cover diagnosis and treatment of various seizure types. This group has provided specific suggestions for many common therapeutic dilemmas. Extensive summary information on specific AEDs is provided, in contrast to other guidelines.

Agency for Healthcare Research and Quality Evidence Report

In 2001, the Agency for Healthcare Research and Quality released the document Management of Newly Diagnosed Patients with Epilepsy: A Systematic Review of the Literature. This review addresses diagnosis of epilepsy, treatment strategies, monitoring of AEDs, and social support of the newly diagnosed patient. This guideline emphasizes that clinical and pharmacological expertise is important in management of patients with epilepsy. However, no definite patient outcomes have been associated with clinical or pharmacological expertise in well-performed studies. The Agency for Healthcare Research and Quality recommends this expertise for selecting optimal AEDs based on epilepsy diagnosis and patient characteristics, adjusting drugs and dosages to reduce seizures, monitoring and limiting adverse drug reactions and interactions, monitoring patients' tolerance and compliance with particular drug regimens, recognizing changes in seizure characteristics, and ordering and interpreting appropriate laboratory tests based on knowledge of specific adverse events associated with different drugs. Also, tailoring AEDs to specific patients, such as women of childbearing age, may be considered as part of clinical and pharmacological expertise. The report stops short of naming particular professionals as having this expertise; however, the authors appear to consider only physicians and not pharmacists as candidates to be clinical and pharmacological experts.

The Agency for Healthcare Research and Quality prepared another report titled Management of Treatment-resistant Epilepsy in 2003. This document defines treatment-resistance and reviews diagnostic methods to determine resistance. Several appropriate and interesting questions are posed concerning treatment of patients with resistance. However, none of them could be answered based on currently available literature.

Abbreviations

American Academy of Neurology Practice Parameters

The American Academy of Neurology published practice parameters discussing more specific topics than the guidelines of the other national bodies. The two most recent practice parameters, Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment of New-onset Epilepsy and Efficacy and Tolerability of the New Antiepileptic Drugs, II: Treatment of Refractory Epilepsy, offer guidance for the use of the newer AEDs: gabapentin, lamotrigine, levetiracetam, topiramate, tiagabine, oxcarbazepine, and zonisamide. These companion papers provide a brief description of each AED, review the studies that support their use in either newly diagnosed or refractory epilepsy, and provide recommendations for their use in specific types of epilepsy. These practice parameters are a useful summary of the evidence for the uses of each of the newer AEDs but do not provide much guidance for managing patients taking these AEDs.

Although published in 1998, much of the information in the American Academy of Neurology Practice Parameter: Management Issues for Women with Epilepsy" remains valid today. This guideline focuses on issues of contraception, and AED treatment during and after pregnancy. Another practice parameter, "A Guideline for Discontinuing Antiepileptic Drugs in Seizure-free Patients," was published in 1996. This guideline specifically addresses the decision criteria to discontinue AEDs but does not offer direction for the tapering of the drug.

Effectiveness

The American Academy of Neurology reviewed the effectiveness of the newer AEDs for treatment of either newly diagnosed or treatment-resistant epilepsy. Sufficient evidence was not available to recommend all of the drugs. The recommendations for the treatment of newly diagnosed patients is summarized as follows: standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital; or the new AEDs, such as lamotrigine, gabapentin, oxcarbazepine, or topiramate. In adults with refractory epilepsy, the recommendations are as follows: gabapentin, lamotrigine, topiramate, oxcarbazepine, levetiracetam, and zonisamide are appropriate as add-on therapy; oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy; and topiramate may be used for the treatment of refractory generalized tonic-clonic seizures.

Treatments of Choice in Special Populations

In the adult population with epilepsy, two groups should receive additional attention in the choice and monitoring of drugs. Women with epilepsy experience specific problems that are not common to men with epilepsy. These problems include decreased fertility; the risk of congenital anomalies and malformations in children of women with epilepsy; changes necessary in management during pregnancy and postpartum; contraceptive efficacy; and catamenial epilepsy. For elderly patients with epilepsy, physiological changes, comorbid conditions, and adverse effects can influence treatment choices. Information regarding these populations is presented in the following sections.

Women with Epilepsy

Women with epilepsy have become a population of interest with the attention being given to general women's health issues. Particular issues relevant to this population include decreased fertility, congenital anomalies and malformations, management surrounding pregnancy, contraception, and catamenial epilepsy. In contrast to past management of women with epilepsy when surgical sterilization was often recommended, women with epilepsy today can expect to have and care for children, if they desire to do so.

Decreased Fertility. In most studies, fertility rates have decreased in women and men with epilepsy. The fertility rates of these women and men are estimated to range between one-third and two-thirds the fertility rate of the population without epilepsy. Reasons for decreased fertility are varied and largely hypothetical, including decreases in marriages and subsequent childbearing, anovulation, early menopause, and sexual dysfunction. The cause of the decreased marriage rate may be multifactorial and may include societal and even health care provider perceptions regarding the ability of people with epilepsy to parent, the genetic transmission of epilepsy, or the risk of fetal abnormalities.

Women with epilepsy may not ovulate as frequently as women without epilepsy. As many as 33% of menstrual cycles in women with epilepsy occur without ovulation compared with 10% in women without epilepsy. Among AEDs, only valproate has been associated with a high percentage of anovulation (55% of women with epilepsy who take valproate are anovulatory). Women with epilepsy also may experience menopause prematurely.

Enzyme-inducing AEDs may also be associated with reduced serum concentrations of estradiol, testosterone, and dihydroepiandrostenedione. Valproate, because of its enzyme-inhibiting properties, can cause increases in androgen serum concentrations. These hormonal changes may contribute to the suspected higher prevalence of polycystic ovary syndrome in women with epilepsy. Epidemiological studies concerning this disease in women with epilepsy are sketchy, but 26–40% of women with epilepsy may have polycystic ovary syndrome, with the higher range associated with valproate treatment. Only 7% of women of reproductive age without epilepsy are affected by polycystic ovary syndrome. In women who are taking valproate, the syndrome may be reversible with discontinuation of the drug.

Risk of Congenital Anomalies and Malformations. For women with epilepsy, the risk of stillbirths (1.3–14%) and neonatal death (1.3–7.8%) is higher than in women without epilepsy (1.1–7.8% and 1–3.9%, respectively). Many authors distinguish between congenital anomalies (any deviation from normal morphology that does not require intervention) and congenital malformations (physical defects requiring medical or surgical intervention and resulting in a major functional disturbance). Fetal

Morrell MJ, Giudice L, Flynn K, et al. Predictors of ovulatory failure in women with epilepsy. Ann Neurol 2002;52:704–11.

anomalies generally involve the midface and distal digits of infants. Health care providers have attempted to group these anomalies into specific syndromes associated with various AEDs, such as fetal hydantoin syndrome or fetal carbamazepine syndrome. In a large, cohort study, no specific defect could be associated with a single AED. Therefore, the anomalies are manifestations of fetal anticonvulsant syndrome.

Infants exposed to AED monotherapy in utero have about twice the rate of congenital malformations (4–6%) as unexposed infants (2–3%). Thirty percent of these malformations are orofacial clefts (i.e., cleft lip or cleft palate). Most serious among the congenital malformations are neural tube defects (primarily myelomeningocele, spina bifida, and anencephaly). These malformations generally occur between weeks 3 and 4 of gestation. Although these conditions can occur with many of the AEDs, the two most commonly implicated are valproate (1–2% of babies of women with epilepsy on valproate have malformations) and carbamazepine (0.5%). These rates are low, but are a definite increase over the 0.06% in the general population. There is some evidence of a relationship between higher doses of valproate and risk of spina bifida. Supplementation with folic acid in women with a history of neural tube defects decreases the risk of neural tube defects. However, it is not clear that folic acid also is protective for women with epilepsy.

Congenital malformation and anomaly risk reduction should be addressed with careful discussion of these risks before pregnancy in all women of childbearing age with epilepsy. The planning of conception should be done in conjunction with the neurologist and obstetrician. When a woman with epilepsy is ready to consider conception and if AED therapy is necessary, it should be the smallest effective dose. Use of at least 1 mg of folic acid should be implemented before conception; the most convenient formulation for this is a prenatal multivitamin.

Management During Pregnancy. About 25–33% of women with epilepsy experience an increase in seizures during pregnancy. There is some evidence that this increase is related to low-serum AED concentrations. When the dose necessary for the AED in question is determined, a serum concentration of the unbound drug should be obtained (or total AED if it is not highly protein-bound). This concentration can be used as a target for therapeutic drug monitoring as the pregnancy progresses. Many health care providers obtain a monthly serum drug concentration to aggressively monitor pregnant women with epilepsy. In addition, good drug adherence should be stressed during pregnancy to prevent fetal harm from a maternal seizure.

Hemorrhagic disease of the newborn is thought to be caused by induction of the liver enzymes responsible for metabolism of the vitamin K-dependent coagulation factors. Phenytoin may also compete with vitamin K for transport across the placenta. Some neurologists begin vitamin K 10 mg/day in the ninth month of pregnancy to prevent neonatal hemorrhage.

Postpartum Management. Breastfeeding should be encouraged in women with epilepsy; however, mothers treated with phenobarbital should be cautioned regarding infant sedation while breastfeeding. Although epilepsy does not render a woman unfit to mother a child in any way, some safety recommendations are necessary for new mothers to protect the baby in the event of a seizure. These recommendations include not sleeping with the baby; changing and dressing the baby only in a position that minimizes risk of fall (e.g., strapped to a changing table, on a wide bed, on the floor); bathing the baby only with assistance; and using a stroller around the home to avoid dropping the baby or falling on top of it. In addition, the new mother should avoid sleep deprivation as much as possible to prevent seizure precipitation. She should also take her AEDs on her usual schedule.

Contraception. Barrier methods of contraception and natural family planning both work as well in couples with epilepsy as in those without epilepsy. Hormonal-based contraception can be affected by the following AEDs: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and topiramate. If hormonal contraception is desired, use of a barrier method in addition to the hormonal contraceptive or use of a formulation with at least 50 mcg of estrogen content is recommended. There are reports of unplanned pregnancies in women using oral contraceptives with 50 mcg of estrogen and enzyme-inducing AEDs.

Catamenial Epilepsy. Estimates of the number of women with catamenial epilepsy vary considerably depending on the methods used to ascertain cases. With careful examination of the menstrual cycle and seizure calendars, some estimates are as low as 10% of women studied. In studies that rely solely on patient perception, reports have been as high as 78% of women studied. Some studies have documented that women with catamenial epilepsy generally have a decrease in the number of seizures experienced after menopause. Of interest, the perimenopausal period is often associated with an increase in seizures for these women.

Several approaches have been developed to treat women with clear catamenial epilepsy based on the cyclical nature of their seizures. However, none of these approaches has been examined in a rigorous, scientific fashion. Acetazolamide has been used at 4 mg/kg given in 1–4 divided dosages for 5–7 days before and during menses. Benzodiazepines also have been used in a cyclical fashion to prevent catamenial seizures. The practical aspect of giving drugs intermittently is frequently overlooked. To provide adequate coverage for many women who report catamenial epilepsy, it would be necessary to treat them for 2 weeks of a typical 28-day menstrual cycle. Therefore, what appears a reasonable strategy in a textbook often becomes impractical in practice. Many health care providers simply treat the woman with a higher dose of a conventional AED every day. This practice has led some investigators to examine the

Zahn CA, Morrell MJ, Collins SD, Labiner DM, Yerby MS. Management issues for women with epilepsy: a review of the literature. Neurology 1998;51:949–56.

Rosciszewska D. Analysis of seizure dispersion during menstrual cycle in women with epilepsy. Monogr Neural Sci 1980;5:280–4.

Table 1-14. Antiepileptic Drugs that Cause Urinary Incontinence

Antiepileptic Drug	Incontinence Type(s)	Proposed Mechanism(s)
Benzodiazepines	Urge, functional	Relaxes bladder sphincter, uninhibited bladder contractions, and sedation
Carbamazepine	Overflow	Parasympathetic detrusor stimulation
Gabapentin	Unknown	CNS micturition stimulation
Phenobarbital	Urge, functional	Relaxes bladder sphincter, uninhibited bladder contractions, and sedation
Phenytoin	Urge, overflow, stress	Blocks α-adrenergic receptors

CNS = central nervous system.

possibility of hormonal approaches. One small study of 14 women using depot injections of medroxyprogesterone acetate demonstrated a decrease in overall seizure frequency of 39%.

Elderly

Antiepileptic drugs are used in about 11% of nursing home residents. The elderly patient with seizures presents a number of potential challenges for the pharmacist. In addition to the commonly known physiological changes that affect the pharmacokinetics of AEDs, the elderly have more comorbid conditions and take more drugs compared with younger populations. Therefore, there is the potential for increased adverse effects and drug-drug interactions. In addition, the elderly may have fewer financial resources than younger patients and the burden of epilepsy may tax these resources.

Physiological Changes. Well-recognized physiological changes in the elderly are reduced renal function, decreased serum albumin, and reduced liver mass and blood flow. Many AEDs can be affected by these changes. With regard to reduced organ function, the best advice is to keep the possibility of decreased metabolism and elimination in mind and to reduce the starting and titration doses of AEDs accordingly. The AEDs with higher protein binding such as phenytoin and valproic acid may need to be monitored with free serum concentrations to account for the lower serum albumin in the elderly patient. However, if the patient is stable, it may be acceptable to calculate the free fraction for that patient, and then apply the free fraction to the total concentration. A formula to adjust the total serum concentration to account for the decreased albumin is as follows:

$$\text{Adjusted concentration} = \frac{\text{observed concentration}}{(0.25 \times \text{albumin}) + 0.1}$$

Comorbid Conditions. Consideration also should be given to any comorbid conditions that are present. As might be expected from the ability of stroke to cause seizures in the elderly, common comorbid diseases include hypertension, stroke, and cardiac disease. The decreased cognition that is seen in some elderly patients may be accentuated by the addition of AEDs. However, many AEDs have beneficial effects that may be useful to treat other comorbid conditions such as migraines and bipolar disorders (Table 1-9).

Adverse Effects. Elderly patients may be more sensitive to adverse effects than the younger population. The AEDs cause 9% of all adverse drug reactions in the elderly population. Data from a Veterans Administration cooperative study showed that 20% of the largely elderly group of patients were unable to tolerate the first AED they were prescribed. In this study, only 47.8% of patients completed 1 year of treatment with 19.4% of patients withdrawing due to adverse effects.

Urinary incontinence is one adverse effect of AEDs that deserves particular mention in the elderly. Although an uncommon adverse effect in the younger population, it may be underappreciated in the elderly. Associations and theoretical mechanisms of this adverse effect are given in Table 1-14.

Discontinuation of an AED in Seizure-free Patients

Patients will often inquire how long they must take an AED or, if they have been seizure-free, when they can stop the AED. The Quality Standards Subcommittee of the American Academy of Neurology issued a Practice Parameter in 1996 that provided guidelines for this situation. Patients with the greatest chance for successful AED cessation are those who are seizure-free during treatment with AEDs for 2–5 years; have a single type of partial or generalized seizure; have a normal neurological examination and normal intelligence quotient; and have an EEG that normalized with treatment. Adults that meet all of these criteria have a 61% chance of successful withdrawal. The longer a patient is seizure-free on AED therapy, the higher the likelihood that he or she will remain seizure-free without therapy; this relationship is also supported by the evidence. Another indicator of ability of the patient to remain seizure-free is whether or not seizures occurred after initiating AED therapy. If the seizures ceased, the patient was more likely to remain seizure-free. Before stopping AEDs, patients also should understand the risks of seizure recurrence, including social and emotional consequences.

If AED withdrawal is attempted, the procedure should be slow with careful monitoring for any seizure activity. The general rule of thumb is to decrease the total daily dose of AED by one-third for 1 month, then by another one-third for month 2, then discontinue the drug. If patients are on more than one AED, each drug should be withdrawn individually. Some health care providers recommend that patients not

11.Lackner TE. Strategies for optimizing antiepileptic drug therapy in elderly people. Pharmacotherapy 2002;22:329–64.

12.American Academy of Neurology. Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients—summary statement. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1996;47:600–2.

engage in any activity that might pose a safety risk during AED discontinuation (e.g., driving).

Monitoring

Following therapy initiation, monitoring is the next step in the care plan for the patient. The pharmacist is uniquely trained and positioned to monitor AED therapy. Therapeutic drug monitoring is important for AEDs and is discussed below. Changes in bone are an underrecognized adverse effect of AED therapy. Common concerns are presented in the following section. Hypersensitivity occurs more often with AEDs than with any other drug class. For this reason, a discussion of the incidence and management of hypersensitivity is included in the following section. Adherence is not a unique problem to epilepsy; nonetheless, the pharmacist should be alert to the possibility of "therapeutic failure" because of nonadherence, discussed in the following section.

Therapeutic Drug Monitoring

Therapeutic ranges of serum concentrations for many AEDs have been established because serum concentrations correlate with central nervous system drug concentrations and, therefore, can be used to help predict seizure control. The best time to obtain serum concentrations for most AEDs is before administration of a dose (trough concentration), because of variations in absorption and inability to predict peak times for many of the AEDs. Reasons for monitoring serum AED concentrations include the following: The expected therapeutic effect is not observed; possible AED-associated toxicity occurs; patient noncompliance is suspected; serum concentrations after a loading dose or at steady-state need to be determined; or drug interaction with another drug is suspected.

In addition, serum concentrations are obtained to determine whether dosage adjustment is needed when weight changes occur and to evaluate altered drug metabolism or elimination in patients with renal, hepatic, or other disease states. For most AEDs, usual laboratory methods for determining serum concentrations (total serum concentration determinations) are adequate; however, for certain highly protein-bound AEDs (e.g., phenytoin, carbamazepine, and valproate), it may be important to obtain free or unbound drug concentrations for selected patients. Obtaining free drug concentrations should be considered when a patient has a total serum concentration within the therapeutic range, but the patient's seizures are uncontrolled or he or she is experiencing AED-associated toxicity. Patients with altered plasma protein binding (malnourished patients or patients with burns, chronic renal failure, liver disease or who are taking drugs that may displace AEDs from protein-binding sites) may require unbound AED serum concentrations.

Bone Effects

Bone disorders, specifically osteoporosis, have been associated with AEDs. Early reports suggested that rickets and osteomalacia were associated with AEDs; however, these studies were conducted in institutionalized patients with multiple risk factors for these conditions. Ambulatory, adult patients appear at little risk for these two problems. Bone mineral density decreases leading to osteoporosis and fractures have been associated with some AEDs (phenobarbital, phenytoin, carbamazepine, and valproate) in both women and men. Newer AEDs have not been systematically evaluated for relationships to osteoporosis at this time. Potential mechanisms of osteoporosis development include increased catabolism of vitamin D, impairment of calcium absorption, impaired bone resorption and formation, hyperparathyroidism, vitamin K deficiency, and calcitonin deficiency.

Osteoporosis is of particular concern in patients with epilepsy because of the increased risk of fractures during seizures. Experts recommend dual-energy x-ray absorptiometry every 5 years during AED treatment in men and premenopausal women and before AED initiation in postmenopausal women. Treatment with vitamin D at doses of 400–4000 IU/day, calcium supplementation, bisphosphonates, or calcitonin may be necessary. Estrogen can increase seizures in some women with epilepsy and is usually not recommended for osteoporosis treatment.

Hypersensitivity

Cutaneous reactions are reported in 2–13% of all patients receiving AEDs. Although these rashes are usually benign and resolve with cessation of the AED, some cutaneous reactions may be serious. Skin manifestations can be as severe as Stevens-Johnson's syndrome or a generalized hypersensitivity syndrome with multiorgan system problems. One potentially confusing issue regarding hypersensitivity to AEDs is the time of onset. Many of these reactions do not appear until several weeks after exposure to the AED. Although a rash can begin as early as after a few days of treatment, the majority occur between 1 and 8 weeks of therapy.

Rash due to lamotrigine can be life-threatening and is associated with faster titration rates. An unusual feature of lamotrigine-associated rash involves the coadministration of valproic acid. Because valproic acid inhibits the metabolism of lamotrigine, a higher lamotrigine serum concentration results. Therefore, the incidence of rash increases when valproic acid is included in the AED regimen. In epilepsy clinical trials, 1% of patients taking lamotrigine with valproic acid were hospitalized due to rash, compared with 0.16% of those taking lamotrigine without valproic acid. If this combination is required, the titration of lamotrigine is slowed considerably (Table 1-11).

A chart review of 1875 adult exposures to AEDs revealed a 4.5% rate of rash development for phenytoin, 5.7% for carbamazepine, 2.4% for phenobarbital, and 5.9% for lamotrigine. Of note, most of the newer AEDs were not approved at the time of this study. This study also demonstrated a high cross-reaction rate for rash between phenytoin and carbamazepine. Of patients switched from phenytoin to carbamazepine due to rash, the percentage of rash development with carbamazepine was 58%; of those switched from carbamazepine to phenytoin, rash appeared in 40% while receiving phenytoin. Several issues remain unresolved regarding AED-induced rash: Whether the AED should be abruptly discontinued to avoid worsening of the

Pack AM, Gidal B, Vazquez B. Bone disease associated with antiepileptic drugs. Cleve Clin J Med 2004;71(suppl 2):S42–48.

reaction or be quickly tapered to avoid precipitating seizures; whether the reaction should be completely resolved before adding a different AED or beginning a new AED immediately?

Adherence

Adherence with a drug regimen can be a problem for any disease state and any drug. One study examined adherence with AEDs using prescription vial caps with microprocessors inside to record the times during the day that the bottle was opened. The percentage of time the patients took medications scheduled 2 times/day with the correct frequency was 86–89%. As expected, this percentage declined with more frequent dosages: adherence was 80% for 3 times/day and 4 times/day regimens. Patients did not do as well with dosing interval. The percentage of time for which doses were spaced appropriately (with a 2-hour allowance on either side of the target dose time) was 59–66% for 2 times/day regimens, 40% for 3 times/day regimens, and 33% for 4 times/day regimens. Because this determination of adherence was in the setting of a clinical trial, adherence may have been somewhat better than in everyday practice.

Patients may be nonadherent with their AED regimen for a variety of reasons that may be grouped as either intentional or unintentional nonadherence. Reasons for intentional nonadherence can be complex. Patients may simply deny that they have a seizure disorder. Some patients are concerned about the social implications of taking medicine in a public setting and of needing to explain that they have epilepsy. Some patients have difficulty with adverse effects and may reduce or completely omit doses of their AED to reduce the adverse effects. Some patients cannot afford their medication and may reduce or omit doses to "stretch" their supply. Others, particularly intractable patients, may feel that the medication is not effective and so do not take their doses. Women may discover they are pregnant and may discontinue their AEDs for fear of harming the fetus.

Unintentional nonadherence may result if the patient does not understand the directions for taking the AED. One common misconception is that the medication should be taken only when seizures occur, and not on a scheduled basis. Other patients may forget doses during the day due to their schedules. When other individuals are responsible for administering some doses such as in an adult day care, the directions for administration may have been miscommunicated when relayed to the caregiver. Patients with memory problems may forget whether they took their AED or where they put their medicine. The use of simple dosing calendars or pillboxes may help individuals avoid unintentional nonadherence.

System Support for Medication Use Process

Most information regarding patient preferences for organization of their epilepsy care comes from the United Kingdom. Therefore, when interpreting the results, the differences in the health care system structure between the United States and the United Kingdom should be considered. One frequent and recurring complaint by patients is that they do not receive enough information about epilepsy from their health care providers. One revealing study reported specific complaints regarding lack of physician interest in the psychosocial aspects of epilepsy management. Many patients felt that their physicians did not expect them to take an active role in the management of their epilepsy. Some patients also expressed their frustration due to the difficulty in accessing specialist care and having to wait months to see specialists.

Several models of pharmacist care in epilepsy are described in the literature. Functions that the pharmacist fulfills in this setting include taking medication histories, performing directed neurological examinations, ordering laboratory evaluations to monitor AEDs, assessing adverse drug reactions, providing medication counseling, and providing pharmacokinetic consultations. These duties can be performed in conjunction with a comprehensive epilepsy care center or on a consultative basis.

Documentation That the Pharmacist Should Perform

Good pharmaceutical care programs rely on documentation through chart notes for individual patients, or through large outcomes studies on a population of patients. The pharmacist should become proficient in the clinic note-writing process and practice it faithfully to supply documentation for services provided to individual patients. Use of notes to document activities is important for good continuity in patient care, for appropriate billing and reimbursement, and for legal issues.

To document population-based outcomes, the pharmacist must first decide on the outcomes to be measured. In the management of epilepsy, the most common clinical outcome is a decrease in number of seizures. Other important outcomes may be reduction of AED-related adverse effects and improved QOL. From an economic standpoint, documentation of pharmacoeconomic benefits from the pharmacist's services can be very important for reimbursement. Patient and physician satisfaction measures also may be important outcomes. All of these outcomes may be documented in the same population of patients but documentation can be time-consuming. To lessen the time burden, a pharmacist may select one or two of these outcomes to measure for initial outcomes documentation, depending on the practice situation.

Patient Education

Patient education is a concern common to all heath care providers caring for patients with epilepsy. Only in the past decade has it become clear that patient education involves more than understanding what to do in case of a seizure and how medications should be administered. Currently, the focus of education is increasing the patient's QOL, reducing the stigma associated with epilepsy, and meeting the patient's goals. Traditional methods of patient education,

Cramer J, Vachon L, Desforges C, Sussman NM. Dose frequency and dose interval compliance with multiple antiepileptic drugs during a controlled clinical trial. Epilepsia 1995;36:1111–7.
Elwyn G, Todd S, Hibbs R, et al. A 'real puzzle': the views of patients with epilepsy about the organisation of care. BMC Fam Pract 2003;4:4.

including counseling regarding epilepsy and AEDs, choosing appropriate dosage forms, and minimizing adverse effects, are some of the means by which patient education goals can be met.

Reducing the Patient's Perceived Burden of Illness

Stigma can be a significant factor that should not be overlooked when caring for the patient with epilepsy. The earliest epilepsy treatments, such as bleeding, emesis, and casting out demons, illustrate the stigma associated with epilepsy. In the 1800s, patients with epilepsy were commonly confined to asylums or hospitals. This negative image of seizures still persists for some people.

The amount of stigma that patients with epilepsy have appears to be related to the number of seizures that the person experiences. In one study, patients experiencing many seizures were 3 times more likely to feel highly stigmatized than patients who were seizure-free. The stigma that patients experience can affect their QOL. Several interesting studies investigating QOL in epilepsy have been conducted.

Quality of life in epilepsy is an individual's perception of the impact of his or her epilepsy condition and treatment on physical and psychological health, level of independence, and social relationships. Measures of QOL reflect discrepancy between the person's actual and desired states. One study asked patients with moderately severe epilepsy to list their concerns about living with recurrent seizures. The top 10 concerns were driving, independence, employment, social embarrassment, drug dependence, mood/stress, safety/injury, drug side-effects, recreation, and social life. Another study conducted in several European countries asked patients how much they worried about their epilepsy. Forty-eight percent of respondents stated that they either worried a lot or some about their condition.

A consistent finding across time and cultures was that QOL decreased with an increase in seizures, with the greatest increase in QOL occurring when patients became seizure-free. A survey conducted in the United Kingdom of 676 patients with epilepsy found that anxiety was more common in patients with one or more seizures each month (21%) than in those without seizures (4%). Seizure frequency was also found to effect a significant change in several QOL domains (e.g., social activity, perception of overall health, standard of living, plans for the future, relationships with friends, feelings of self, personal fulfillment, and stigma), and decreased QOL was associated with increased number of seizures. Another study conducted in England found some factors were independently associated with a general QOL of "not happy." These factors were epilepsy attack in the previous year, patients feeling as if they were treated "like an inferior person" by some people, other long-term health problems, and male gender. The patients with lower QOL also were the higher users of the health care system.

One literature review described several important and consistent findings with regard to QOL: 1. QOL is worse in patients with epilepsy than in the general population; 2. QOL in patients with epilepsy is comparable to or worse than in patients with other chronic medical conditions; 3. QOL is similar to that of healthy persons when epilepsy is well-controlled; 4. frequency of seizures seems to be one of the most relevant determinants of poor QOL scores; and 5. depression worsens QOL in patients affected by epilepsy.

Given that QOL improves with epilepsy control, the effect of various treatment options on QOL becomes important. Antiepileptic drugs may have either a positive or a negative effect on QOL. This seemingly ambiguous statement reflects patients' assessments of the balance between seizure control and AED adverse effects. Epilepsy surgery generally results in a more positive QOL, and this finding is correlated with the degree of seizure control that results from the surgery.

Although QOL assessments have been measured with generic instruments in patients with epilepsy, more responsive measures come from instruments specifically designed to measure QOL in epilepsy. The most commonly used scales in the United States are the Washington Psychosocial Seizure Inventory, the Epilepsy Surgery Inventory-55, and the QOL in Epilepsy scales. Few comparisons between the scales have been conducted. One comparison of the Epilepsy Surgery Inventory-55 and the Washington Psychosocial Seizure Inventory found the Epilepsy Surgery Inventory-55 much more responsive to changes in treatments and emotional well-being, and health perceptions.

The original QOL in Epilepsy scale has 89 items, but two shorter scales have been developed with 31 and 10 questions. These shorter tools can be more practical to administer when time is short. One comparison of these scales showed that the shorter epilepsy-targeted measure does not compromise responsiveness. Another comparison study determined the minimum important change for the QOL in Epilepsy-89 and QOL in Epilepsy-31 scales and the ability of these scales to accurately distinguish between minimum, medium, and large changes in clinical condition. The minimum important change was 10.1 for QOL in Epilepsy-89 and 11.8 for QOL in Epilepsy-31 with high accuracy to distinguish between minimum important change and medium or large change. For the special case of adults with epilepsy and mental retardation, the Glasgow Epilepsy Outcome Scale has been developed. It is a 35-item measure of QOL.

Assuring That the Patient's Goals of Therapy are Met

Many health care providers are adept at establishing therapeutic goals for patients, particularly goals that are easily measured such as number of seizures in a given period of time. However, the goals of the patient may not always coincide with those of the practitioner. A small amount of work has been conducted to explore the common therapy goals of patients with epilepsy.

A questionnaire sent to a group of patients with epilepsy in the United Kingdom evaluated the patients' satisfaction with various aspects of their care. To a large extent, patients placed more emphasis on the physician's ease of communication, perceived knowledge of epilepsy, and provision of adequate information on epilepsy than on

Berto P. Quality of life in patients with epilepsy and impact of treatments. Pharmacoeconomics 2002;20:1039–59.

whether the physician was a general practitioner or a neurologist. This information sheds light on the factors that patients identify as important for their care, which could also be their expectations from the pharmacist involved in epilepsy care. Patients prefer a health care provider who not only has a good knowledge of epilepsy and AEDs, but can also communicate this knowledge effectively to the patient in a non-intimidating manner.

Special Directions and Precautions for Drug Preparation, Administration, and Use by the Patient

People of all ages, abilities, and socioeconomic status have epilepsy. Therefore, it is important to consider the special needs of these populations when choosing pharmacotherapy. Patients may have difficulty with some dosage forms, may have financial difficulty paying for some drugs, or may have concomitant disease states that dictate therapeutic choice.

Antiepileptic drugs are available in many dosage forms to meet the needs of most patients (Table 1-9). Sprinkle capsules are marketed by several manufacturers to provide dosage forms for those patients who cannot swallow tablets or capsules. Sprinkle capsules should be opened and the contents sprinkled on soft food, such as pudding or applesauce. They should not be chewed, but should be simply swallowed.

Administration of AEDs through feeding tubes can usually be accomplished with liquid dosage forms. Phenytoin suspension is notorious for being difficult to suspend by gentle shaking. To avoid the potential for radically different doses, significant patient or caregiver education or single-dose packaging should be used. When AEDs are administered with continuous enteral feedings, there exists a significant potential for decreased drug absorption. When an AED is to be administered through a feeding tube, the usual recommendation is to divide the dose into at least two dosages per day, hold the enteral nutrition for 1–2 hours before and after each dose, and flush the feeding tube with water before and after the dose. It also will be necessary to recalculate the rate of the enteral feeding to accommodate this periodic discontinuation.

Slow-release carbamazepine is supplied by two different manufacturers in formulations with two different mechanisms of delayed release. Both products should be administered twice daily. The Shire product, Carbatrol, is a capsule composed of immediate-release beads (25%), extended-release beads (40%), and enteric-release beads (35%). This product can be opened and the contents sprinkled on soft food; however, care should be taken to avoid chewing the beads. Tegretol XR, a Novartis product, uses an osmotic pump release mechanism. This product should not be split, crushed, or chewed. In addition, the shell of the release system is sometimes observed in the stool of patients taking the product. While the Food and Drug Administration Orange Book does not list bioequivalence ratings for these products, studies show that these two products could be considered bioequivalent.

Extended-release divalproex sodium (Depakote ER) is different from the enteric-coated product that is labeled delayed release (Depakote). The extended-release formulation can be administered once daily, whereas the enteric-coated product must be administered at least twice daily. In addition, the extended-release formulation has a bioavailability of 89% compared with the delayed-release formulation.

Drug Costs

The direct annual cost of epilepsy in 1987 was estimated at $1,480 for an adult. For refractory patients, the costs increased substantially to $2,525 annually. Although some older AEDs are inexpensive, the newer drug is expensive. When rational polytherapy is used, $500 or more in monthly medication costs is not uncommon. A particular problem exists for the refractory patient who may have Medicare because of disability related to epilepsy. In many states, the income from the Medicare benefit is too high to qualify for Medicaid assistance for medication. At the time of this writing, there is no Medicare prescription benefit; thus, many patients are faced with the choice of buying necessities or medication. With new legislation, at least some AEDs will be available under Medicare benefits. Further, most AEDs are available through patient assistance programs from pharmaceutical manufacturers.

As part of the patient education process, the pharmacist should determine the patient's ability to procure drugs. If the patient has public or private insurance, the pharmacist should inquire about the extent of the prescription benefit and the amount that will be borne by the patient. If the patient does not have health insurance, the ability of the patient to purchase prescription drugs must be investigated. If the patient does not have resources to obtain drugs, he or she can be introduced to patient assistance programs or other community sources of free or reduced-price drugs.

Specific Issues Related to Drug or Disease-state Counseling in Different Patient Populations

The mentally or multiply disabled patient presents particular difficulties with communication. The patient's abilities should be carefully assessed to avoid excluding the patient during discussions of therapy. Language geared to the patient's comprehension level should be used. For effective counseling in patients with impaired eyesight or hearing, written material with large type may be necessary.

Large-type, written material may be used for elderly patients to supplement verbal communication. Slow audible speech can help counseling comprehension in patients with hearing impairment. Patients with memory difficulties may be assisted with drug calendars, portable alarm clocks, pillboxes, and appointment and refill reminders.

Another major factor in the social lives of patients with seizures is the loss of driving privileges. All states have restrictions on driving for patients with uncontrolled epilepsy. Although this restriction can be an incentive for compliance, the patient who has even infrequent seizures is not a candidate for a driver's license. In major metropolitan areas, public transportation is often adequate to meet the needs of many citizens. However, in smaller communities or in rural settings, this restriction on driving may adversely affect the patient's ability to obtain a job or socialize. Most states have mechanisms in place to reinstate the driver's license of a patient who becomes seizure-free. Some

lawsuits against physicians have been successful when there was no documentation that the physician informed the patient of the laws against driving after seizures have been diagnosed. In the initial patient care note, the pharmacist also should document this discussion with the patient.

Quality Improvement

It is important not only to monitor individual patient outcomes and progress towards goals, but also to monitor overall outcomes and quality of a practice, group, or healthcare system. Currently, little monitoring of health care systems is being done in the United States. Fortunately, European guidelines suggest performance measures that could be adopted in some United States practices. For example, the SIGN suggestions for audit regarding treatment are as follows: proportion of patients in which treatment is recommended by a specialist in the area of epilepsy; proportion of patients who are seizure-free; number of patients who are on one-, two-, three-, and four-drug regimens; drug is appropriate for seizure type; information on adverse AED effects is provided and documented; therapeutic drug monitoring is performed only for appropriate indications; discussion is provided on AED withdrawal or continuation in patients who are seizure-free for more than 2 years; and surgery is considered in patients established to be drug-resistant.

Conclusion

Treatment of epilepsy is a complicated venture, requiring the collaboration of health care providers and the patient to achieve optimum outcomes. The pharmacist fits well into this milieu by providing appropriate drug choices for the patient and by helping the patient to integrate therapy into his or her life. The role of the pharmacist continues to expand in this area as more knowledge is gained regarding epileptogenesis and therapy. The pharmacist also can play a role in integration and monitoring at the health system level by incorporating guideline recommendations and quality monitors into the United States health care system.

Annotated Bibliography

1. Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. Epileptic Disord 2004;6:57–75.

   This review article succinctly describes uses of antiepileptic drugs other than epilepsy. It references the primary literature to support its conclusions. Specific attention is given to the use of AEDs for treating patients with trigeminal neuralgia, neuropathic pain syndromes, migraines, essential tremors, and bipolar disorder. Drugs discussed include carbamazepine, gabapentin, valproate, primidone, lamotrigine, oxcarbazepine, gabapentin, and topiramate. This article is especially useful to the practicing pharmacist when choosing an antiepileptic drug for a patient with several comorbid conditions.

2. Foldvary-Schaefer N, Morrel MJ. Epilepsy in women: the biological basis for the female experience. Cleve Clin J Med 2004;71(suppl 2):S1–58.

   This entire supplement is an excellent review of issues regarding women with epilepsy. There are discussions of the effects of hormones on seizure control and reproductive disturbances, management of pregnancy, and bone disease in women with epilepsy. For each disorder, the pathophysiology is discussed, the primary literature is reviewed, and specific recommendations are made for treatment and monitoring. Much of this information is relatively new and unknown to health care providers. It is a good reference for the practicing pharmacist who provides education to patient care teams and directly to patients and their families.

3. Berto P. Quality of life in patients with epilepsy and impact of treatments. Pharmacoeconomics 2002;20:1039–59.

   This article reviews the basic issues of quality of life and their application to epilepsy, including the impact of surgical and pharmacological treatments. The effects of various interventions on both children and adults are described, when available. Primary literature is reviewed to determine common themes regarding quality of life for patients with epilepsy. Clear illustrations are given regarding the improvement of quality of life with improvement in seizure control. The literature on the effect of antiepileptic drug treatment on the quality of life although limited, is clearly explained. The practicing pharmacist may find this reference useful to understand the developing body of literature regarding quality of life for patients with epilepsy. In addition, individuals interested in quality of life research may find this article a useful starting point for development of research.

4. Fisher RS, Vickrey BG, Gibson P, et al. The impact of epilepsy from the patient's perspective II: views about therapy and health care. Epilepsy Res 2000;41:53–61.

   This survey conducted in the United States of 1023 people with epilepsy gives a unique point of view regarding the impact of epilepsy and its treatment on patient outcomes related to quality of life. The selection of subjects was not completely random and may have included individuals more interested in their disease state and its treatment than the overall population of subjects with epilepsy. Particularly interesting to pharmacists are the detailed results regarding drug information needs and adverse effects. About 90% of the respondents were taking drugs for their epilepsy; however, only 68% of respondents were satisfied with their current seizure drugs. Items of most importance to patients were seizure control, adverse effects, convenient dosing regimens, and cost. There were substantial differences in concern about specific adverse effects among the drugs; these differences may play an important role in drug selection. Many respondents indicated an interest in receiving more information about epilepsy, demonstrating a need that pharmacists could fill.

5. Gaitatzis A, Sander JW. The mortality of epilepsy revisited. Epileptic Disord 2004;6:3–13.

   The authors discuss common causes of death in patients with epilepsy in this review article. The information on mortality is summarized in an epidemiological fashion. Three parameters, the mortality rate, the standardized mortality ratio, and the proportional mortality rate, are explained and compared for many risk factors. The authors discuss the relationship of death in patients with epilepsy to the length of

Abbreviations

time since diagnosis. The phenomenon of sudden, unexplained death in patients with epilepsy is discussed in detail. Suicide risks are also evaluated for the epilepsy population. The practicing pharmacist may find this article useful in understanding the epidemiological terminology used in the epilepsy literature. In addition, this paper may assist the pharmacist in becoming more conversant when patients and other health care providers inquire about increased risk of death with epilepsy and its treatment.