REVIEW ARTICLE

DRUG THERAPY

ALASTAIR J.J. WOOD, M.D., *Editor*

ANTIEPILEPTIC DRUGS

MARTIN J. BRODIE, M.D.,
AND MARC A. DICHTER, M.D.

AT a conservative estimate, 50 million people worldwide have epilepsy. The annual incidence ranges from 20 to 70 cases per 100,000[1] and the point prevalence is 0.4 to 0.8 percent.[2] The incidence rates are highest in childhood, plateau from the age of 15 to 65 years, and rise again among the elderly. Overall, 5 percent of persons report a seizure at some time in their lives. This figure excludes febrile convulsions, which occur in approximately 5 percent of children. These data suggest that there is a substantial rate of remission, even among persons who never receive treatment with an antiepileptic drug.[3]

About 30 percent of patients with seizures have an identifiable neurologic or systemic disorder,[4] and the remainder have either idiopathic or cryptogenic epilepsy. The diagnosis is based on the description of the seizures and the clinical context in which they occur, often supplemented by the results of electroencephalography. Treatment with an antiepileptic drug is usually begun when the patient has had more than one unprovoked seizure within a year, whatever the type.

CLASSIFICATION OF SEIZURES AND EPILEPTIC SYNDROMES

Epileptic seizures have varied manifestations, ranging from brief lapses of attention (absence seizures) to limited motor, sensory, or psychological changes (partial seizures) to prolonged losses of consciousness with convulsive motor activity (idiopathic, symptomatic, or localization-related tonic–clonic seizures). It is important to classify the kind of seizure in order to choose the most effective therapy. The current classification of seizures by the International League against Epilepsy[5] is based on the clinical description and electroencephalographic pattern (Table 1). The league's complementary classification of epileptic syndromes (Table 2) takes into account such factors as the age of the patient, type of seizure, presence or absence of an underlying neurologic lesion, and presence or absence of a family history.[6]

From the Epilepsy Research Unit, University Department of Medicine and Therapeutics, Western Infirmary, Glasgow, Scotland (M.J.B.), and the Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia (M.A.D.). Address reprint requests to Dr. Brodie at the Epilepsy Research Unit, Department of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT, Scotland.

INDICATIONS FOR TREATMENT

Most patients with recurrent epileptic seizures require treatment. The exceptions are patients with provoked seizures and those with episodes separated by years. The question of whether to treat a single seizure is controversial. Patients who have had an unprovoked seizure have a substantial chance of recurrent events (i.e., epilepsy), with the frequency ranging from 31 to 71 percent, depending on other risk factors.[7,8] Patients with an underlying neurologic abnormality or cerebral lesion or a specific syndrome, such as juvenile myoclonic epilepsy, should probably be treated.

The decision about treatment with antiepileptic drugs should be made after an extensive discussion with the patient about the risks and benefits of treatment and of no treatment. The best drug for the particular type of seizure is selected and administered in a dose high enough to bring the plasma drug concentration into a target (therapeutic) range without unacceptable side effects. The goal should be the restoration of a normal life through complete control of seizures with the use of a single drug that has no side effects.

CHOICE OF DRUG

Carbamazepine, phenytoin, valproic acid, phenobarbital, and primidone are all effective in reducing the frequency of partial seizures.[9,10] There are conflicting data on whether carbamazepine is more effective than valproic acid.[10-14] Carbamazepine and phenytoin are the drugs of choice for partial seizures. In Europe, some clinicians choose valproic acid instead of phenytoin, because of the relative tendency of the liver to be unable to metabolize the drug load (saturation kinetics), which makes it difficult to use without monitoring the plasma drug concentrations, and because of the perception that phenytoin has more side effects. Phenobarbital is relegated to use as a second-line drug in most cases, since it tends to cause sedation and depression in adults and hyperactivity and aggression in children.

For patients with tonic–clonic seizures, valproic acid, phenytoin, and carbamazepine are all effective. Valproic acid is the drug of choice for patients with tonic–clonic seizures and spike-wave discharges on the electroencephalogram and for patients with other forms of generalized epilepsy, particularly myoclonic jerks and absence seizures. Ethosuximide is also a useful drug for absence seizures. For patients who have both absence seizures and tonic–clonic seizures or myoclonic jerks, valproic acid is preferable.

Substantial data have accumulated on the clinical pharmacokinetics of the established antiepileptic drugs (Table 3). The indications for their use and guidelines for doses in children and in adolescents and adults are

Table 1. International Classification of Epileptic Seizures.

Partial seizures (beginning locally)
Simple partial seizures (without impaired consciousness)
With motor symptoms
With somatosensory or special sensory symptoms
With autonomic symptoms
With psychological symptoms
Complex partial seizures (with impaired consciousness)
Simple partial onset followed by impaired consciousness
Impaired consciousness at onset
Partial seizures evolving into secondary generalized seizures
Generalized seizures (convulsive or nonconvulsive)
Absence seizures
Typical
Atypical
Myoclonic seizures
Clonic seizures
Tonic seizures
Tonic–clonic seizures
Atonic seizures
Unclassified seizures

shown in Tables 4 and 5, respectively. The optimal use of these drugs must be governed by a recognition of their potential dose-related and idiosyncratic toxic effects (Table 6).

Carbamazepine

Carbamazepine is effective for the treatment of partial and generalized tonic–clonic seizures[14] but is not effective, and may even be deleterious, in patients with absence or myoclonic seizures.[15] The drug acts by preventing repetitive firing of action potentials in depolarized neurons[16] through voltage- and use-dependent blockade of sodium channels.[17]

Treatment with carbamazepine should be initiated at low doses (200 to 400 mg daily) to allow tolerance of its central nervous system side effects to develop.[18] The dose can then be increased by increments of 200 mg per day at intervals of two to four weeks until a maintenance dose has been reached that controls the seizure disorder completely. The final dose often depends on the extent to which carbamazepine induces its own metabolism.[19] Diplopia, headache, dizziness, and nausea are the most common side effects of carbamazepine. These symptoms limit the dose in many patients with refractory epilepsy. In addition, high peak plasma concentrations can result in intermittent central nervous system side effects about two hours after ingestion of the drug, necessitating administration three or four times daily in some patients. This problem can be overcome by prescribing a controlled-release formulation, now widely available in Europe and the Far East, which can be given once[20] or twice[21] daily.

Carbamazepine can cause a range of idiosyncratic reactions; the most common is a morbilliform rash, which develops in about 10 percent of patients.[14] Less common skin eruptions include erythema multiforme and the Stevens–Johnson syndrome. Reversible mild leukopenia is common but does not require discontinuation of therapy unless there is evidence of infection or the leukocyte count falls below 2,000,000 per cubic millimeter. Blood dyscrasias and toxic hepatitis are rare. At high plasma concentrations, carbamazepine has an antidiuretic hormone–like action; the resulting hyponatremia is usually mild and asymptomatic, but if the plasma sodium concentration falls below 125 mmol per liter, there may be confusion, peripheral edema, and decreasing control of seizures.[14] Orofacial dyskinesias and cardiac arrhythmias are additional rare side effects.

In addition to inducing its own metabolism, carbamazepine can accelerate the hepatic oxidation and conjugation of other lipid-soluble drugs.[22] The most common interaction is with oral contraceptive pills, and most women require an increase in the daily dose of estrogen from 35 to 50 μg or more.[23] Carbamazepine also accelerates the metabolism of valproic acid, ethosuximide, corticosteroids, anticoagulant and antipsychotic drugs, and cyclosporine. Paradoxically, whereas phenytoin induces the metabolism of carbamazepine, carbamazepine inhibits the metabolism of phenytoin.[22] Thus, adding phenytoin decreases plasma carbamazepine concentrations by about a third,[24] whereas adding carbamazepine increases plasma phenytoin concentrations by a similar amount.[25,26] Drugs that inhibit the metab-

Table 2. International Classification of Epilepsies and Epileptic Syndromes.

Localization-related (focal, local, or partial) epilepsies and syndromes
Idiopathic epilepsy with age-related onset
Benign childhood epilepsy with centrotemporal spikes
Childhood epilepsy with occipital paroxysms
Symptomatic epilepsy
Generalized epilepsies and syndromes
Idiopathic epilepsy with age-related onset (listed in order of age at onset)
Benign neonatal familial convulsions
Benign neonatal nonfamilial convulsions
Benign myoclonic epilepsy in infancy
Childhood absence epilepsy (formerly known as pyknolepsy)
Juvenile absence epilepsy
Juvenile myoclonic epilepsy (formerly known as impulsive petit mal)
Epilepsy with generalized tonic–clonic seizures on awakening
Other idiopathic epilepsies
Idiopathic or symptomatic epilepsy (listed in order of age at onset)
West's syndrome (infantile spasms)
Lennox–Gastaut syndrome (childhood epileptic encephalopathy)
Epilepsy with myoclonic–astatic seizures
Epilepsy with myoclonic absence seizures
Symptomatic epilepsy
Nonspecific syndromes
Early myoclonic encephalopathy
Early infantile epileptic encephalopathy
Specific syndromes (epileptic seizures as a complication of a disease, such as phenylketonuria, juvenile Gaucher's disease, or Lundborg's progressive myoclonic epilepsy)
Epilepsies and syndromes with both generalized and focal seizures
Neonatal seizures
Severe myoclonic epilepsy in infancy
Epilepsy with continuous spike waves during slow-wave sleep
Acquired epileptic aphasia (Landau–Kleffner syndrome)
Epilepsies without unequivocal generalized or focal features*
Special syndromes
Situation-related seizures
Febrile convulsions
Seizures related to other identifiable situations, such as stress, hormonal changes, drugs, alcohol withdrawal, or sleep deprivation
Isolated, apparently unprovoked epileptic events
Epilepsies characterized by specific modes of seizure precipitation
Chronic progressive epilepsia partialis continua of childhood

*This category includes cases in which the clinical and electroencephalographic findings do not permit classification of the epilepsy as clearly generalized or localization-related, such as cases of tonic–clonic seizures during sleep.

Table 3. Pharmacokinetics of Established Antiepileptic Drugs.

Drug	Absorption (% Bioavailability)	Protein Binding (%)	Elimination Half-Life (hr)	Route of Elimination	Comments
Carbamazepine	Slow (75–85)	70–80	8–24 (with multiple doses)	Hepatic metabolism (active metabolite)	Enzyme inducer, autoinduction of metabolism
Phenytoin	Slow (85–95)	90–93	9–40	Saturable hepatic metabolism	Enzyme inducer, concentration-dependent elimination half-life
Valproic acid	Rapid (100)	88–92	7–17	Hepatic metabolism (active metabolites)	Enzyme inhibitor, concentration-dependent protein binding
Phenobarbital	Slow (95–100)	48–54	72–144	Hepatic metabolism (25% excreted unchanged)	Enzyme inducer, sedative effect, development of tolerance
Primidone	Rapid (90–100)	20–30	4–12	Hepatic metabolism (active metabolites, 40% excreted unchanged)	Sedative effect, phenobarbital as a metabolite, development of tolerance
Ethosuximide	Rapid (90–95)	0	20–60	Hepatic metabolism (25% excreted unchanged)	More rapid clearance in children
Clonazepam	Rapid (80–90)	80–90	30–40	Hepatic metabolism	Sedative effect, development of tolerance, rebound effect

olism of carbamazepine sufficiently to cause toxic effects include cimetidine, propoxyphene, diltiazem, erythromycin, isoniazid, and verapamil. The less common neurotoxic interaction with lithium (resulting in confusion, disorientation, drowsiness, ataxia, tremor, and hyperreflexia) is not associated with altered plasma concentrations of either drug.[27]

The substantial between-dose variation in plasma carbamazepine concentrations — as much as 100 percent with twice-daily doses[19] — makes their interpretation problematic. In many patients, the dose can be titrated adequately with the use of clinical criteria alone.[28] Exceptions include patients in whom noncompliance is suspected and those taking other antiepileptic drugs likely to interact with carbamazepine.

Phenytoin

Phenytoin is effective for the treatment of partial and tonic–clonic seizures. It appears to act by inducing voltage- and use-dependent blockade of sodium channels.[29,30] Phenytoin is one of a handful of drugs for which the kinetics change from first order (in which the extent of metabolism is directly correlated with the amount of available drug) to saturation at therapeutic doses.[31] Accordingly, at plasma concentrations of about 15 μg per milliliter, a moderate increment in the dose can cause an unexpectedly large rise in the plasma concentration. A starting dose of 5 mg per kilogram of body weight raises plasma concentrations within the target range of 10 to 20 μg per milliliter in most patients, but some will have higher concentrations and neurotoxic effects. Other patients require a higher dose — for example, those who abuse alcohol and have increased hepatic microsomal enzyme activity. In general, the dose can be increased by 100 mg if the plasma drug concentration is 8 μg per milliliter or less, but no more than 50 mg should be added if the plasma drug concentration is higher. Some patients can benefit from plasma concentrations above 25 μg per milliliter, without adverse effects.

Phenytoin can cause a range of dose-related and idiosyncratic adverse effects (Table 6). Reversible cosmetic changes (gum hypertrophy, acne, hirsutism, and facial coarsening), although often mild, can be troublesome. Neurotoxic symptoms (drowsiness, dysarthria, tremor, ataxia, and cognitive difficulties) become increasingly likely when the plasma drug concentration exceeds 20 μg per milliliter. The diagnosis of phenytoin-related toxicity should be made on clinical grounds. The patient usually reports mental slowing and unsteadiness, and a neurologic examination reveals nystagmus and ataxia. There may also be a paradoxical increase in the frequency of seizures.

Phenytoin can induce the oxidative metabolism of many lipid-soluble drugs, including carbamazepine, valproic acid, ethosuximide, anticoagulant agents, corticosteroids, and cyclosporine.[32] Because its metabolism is saturable, inhibitory interactions are particularly likely to have neurotoxic effects. Drugs that inhibit the metabolism of phenytoin include allopurinol, amiodarone, cimetidine, imipramine, and some sulfonamides. Interactions involving protein-binding displacement are not clinically important unless the displacement is accompanied by enzyme inhibition, producing a rise in plasma phenytoin concentrations, as is the case with valproic acid.[22]

Valproic Acid

Valproic acid is effective in patients with all types of seizures, and especially in those with idiopathic generalized epilepsy.[33] The drug acts by limiting sustained repetitive neuronal firing through voltage- and use-dependent blockade of sodium channels, although it is also likely to have other effects.[34,35] The starting dose for adults and adolescents is 500 mg once or twice daily, with subsequent increases according to the response. Some clinicians prefer to administer valproic acid three times daily in children because of the risk of gastrointestinal intolerance and the drug's short elimination half-life.[36] Divalproex sodium (a combination of valproic acid and sodium valproate) can be given twice daily. Because valproic acid can take several weeks to become fully effective, the dose should not be increased sooner.[37] Since there is not a clear-cut relation among

the plasma concentration of valproic acid, its effect, and toxicity and since the daily variation in plasma concentrations is wide, routine monitoring may not be helpful unless it is correlated with the patient's clinical situation. Some patients need and can tolerate plasma concentrations as high as 150 μg per milliliter.

Common side effects of valproic acid are dose-related tremor, weight gain due to appetite stimulation, thinning or loss of hair (usually temporary), and menstrual irregularities, including amenorrhea. Sedation is unusual, although stupor and encephalopathy occur in rare cases, possibly as a consequence of an underlying deficiency of carnitine.[38] The incidence of hepatotoxic effects, histologically evident as a microvesicular steatosis, is less than 1 in 20,000 patients,[39] but such effects are of concern in children under three years of age who are receiving multiple antiepileptic drugs.[40] Approximately 20 percent of all patients receiving the drug have hyperammonemia without hepatic damage.[41] This effect is usually asymptomatic but occasionally can cause confusion, nausea, and vomiting.[42]

Valproic acid can inhibit several hepatic metabolic processes, including oxidation, conjugation, and epoxidation.[22] Targets include other antiepileptic drugs, particularly phenytoin, phenobarbital, carbamazepine epoxide, and lamotrigine. Aspirin displaces valproic acid from its binding sites on plasma proteins and inhibits its metabolism.[43] Valproic acid does not interfere with the action of oral contraceptives.

Table 4. Guidelines for Doses of Established Antiepileptic Drugs in Children.

Drug	Indication	Starting Dose	Standard Maintenance Dose (range)	No. of Doses/Day	Target Plasma Drug Concentration (range)
		mg/kg/day			*μg/ml*
Carbamazepine	Partial and generalized tonic–clonic seizures	5	10–25	2–4	6–12
Phenytoin	Partial and generalized tonic–clonic seizures or status epilepticus	5	5–15	1 or 2	10–20
Valproic acid	Partial seizures or generalized epilepsies	10	15–40	1–3	50–100
Phenobarbital	Partial and generalized tonic–clonic seizures, neonatal seizures, or status epilepticus	4	4–8	1 or 2	10–40
Primidone	Partial or generalized tonic–clonic seizures	10	20–30	1 or 2	5–12
Ethosuximide	Generalized absence seizures	10	15–30	1 or 2	40–100
Clonazepam	Myoclonic epilepsy, Lennox–Gastaut syndrome, infantile spasms, or status epilepticus	0.025	0.025–0.1	2 or 3	None

Phenobarbital

Phenobarbital is as effective as carbamazepine and phenytoin in abolishing partial and generalized tonic–clonic seizures.[9] At the cellular level, it prolongs inhibitory postsynaptic potentials by increasing the mean chloride-channel opening time and hence the duration of γ-aminobutyric acid–induced bursts of neuronal activity.[44] To minimize the sedative effect, the starting dose should be low (60 mg in adults and 4 mg per kilogram of body weight in children) and increased gradually according to the response. The value of measuring plasma phenobarbital concentrations is limited, because the concentration associated with optimal control varies considerably.[28] In addition, the development of tolerance to the drug's central nervous system side effects makes the toxic threshold imprecise.

The main limitation of phenobarbital is its propensity to alter cognition, mood, and behavior. The drug can cause fatigue and listlessness in adults and insomnia, hyperactivity, and aggression in children (and sometimes in the elderly). Memory, mood, and learning capacity may be subtly impaired. Depression, arthritic changes, and Dupuytren's contracture can be associated problems. Tolerance of the deleterious cognitive effects of phenobarbital can develop, but unfortunately, tolerance of its anticonvulsant effect can also develop.[45] Phenobarbital is the archetypal enzyme inducer and can accelerate the metabolism of many lipid-soluble drugs.[46]

Primidone

Primidone is metabolized to phenobarbital and another active metabolite, phenylethylmalonamide. The efficacy of primidone is similar to that of phenobarbital, but primidone is less well tolerated.[9] There is little to recommend this drug over phenobarbital for patients in whom treatment with a barbiturate is contemplated.

Ethosuximide

Ethosuximide is used for patients with uncomplicated absence seizures. It acts by reducing low-threshold, transient, voltage-dependent calcium conductance in thalamic neurons.[47] In children older than six years, 500 mg daily is a reasonable starting dose, with further increments as necessary to a maximum of 1 to 2 g daily. For most patients the dose can be increased every two to four weeks, but more rapid titration may be needed. Infants require relatively higher doses (i.e., 15 to 30 mg per kilogram daily). The need for an adjustment of the dose can be determined clinically or electroencephalographically with telemetry.

The side effects of ethosuximide usually involve the gastrointestinal tract (nausea, vomiting, and abdominal pain) or central nervous system (lethargy, dizziness, and ataxia). These problems are often not correlated with high plasma concentrations of ethosuximide. There have been rare reports of blood dyscrasias, which in some cases have been fatal. The *Physicians' Desk Reference* recommends periodic blood counts,[48] but this recommendation is not universally accepted.[49] The metabo-

Table 5. Guidelines for Doses of Established Antiepileptic Drugs in Adolescents and Adults.

Drug	Indication	Starting Dose	Most Common Daily Dose	Standard Maintenance Dose (range)	No. of Doses/ Day	Target Plasma Drug Concentration (range)
		milligrams				*μg/ml*
Carbamazepine	Partial or generalized tonic–clonic seizures	200	600	400–2000	1–4*	6–12
Phenytoin	Partial or generalized tonic–clonic seizures or status epilepticus	200	300	100–700	1 or 2	10–20
Valproic acid	All generalized seizures or partial seizures	500	1000	500–3000	1 or 2	50–100
Phenobarbital	Partial or generalized tonic–clonic, myoclonic, clonic, or tonic seizures, or status epilepticus	60	120	60–240	1 or 2	10–40
Primidone	Partial or generalized tonic–clonic seizures	250	500	250–1500	1 or 2	5–12
Ethosuximide	Absence seizures	500	1000	500–2000	1 or 2	40–100
Clonazepam	Myoclonic or generalized tonic–clonic seizures or status epilepticus	1	4	2–8	1 or 2	None

*Only one or two daily doses are required with the modified-release formulation.

lism of ethosuximide is altered by enzyme inducers such as phenytoin and carbamazepine and by enzyme inhibitors such as valproic acid.[32]

Clonazepam

Clonazepam is effective in preventing absence seizures, myoclonic jerks, and tonic–clonic seizures.[50] As with other benzodiazepines, however, the sedative effect and the development of tolerance substantially reduce its usefulness. Few patients have good responses, and in nearly 50 percent of patients, the epilepsy is exacerbated when the drug is withdrawn.[51] The therapeutic role of clonazepam is therefore limited, and it is used mostly for refractory myoclonic seizures.

Treatment of Refractory Epilepsy

In about 30 percent of patients with epilepsy, the seizures are refractory to treatment with a single antiepileptic drug.[52] Many of these patients have partial seizures due to an underlying anatomical lesion, and the addition of other drugs is successful only about 10 percent of the time.[53,54] Before long-term treatment with more than one drug is undertaken, all reasonable options for monotherapy should be exhausted. If one drug is ineffective, an alternative drug should be introduced gradually. If the patient has a response to the second drug, an attempt should be made to withdraw the original drug. Only if this attempt is unsuccessful should two-drug therapy be continued. No controlled clinical trials have identified the best second drug or combination of drugs.

For patients with partial or tonic–clonic seizures, most specialists use two of the three first-line drugs — namely, carbamazepine, valproic acid, and phenytoin, for combination therapy, although their mechanisms of action overlap.[55] For patients with myoclonic seizures who do not have a response to valproic acid, clonazepam can be added, whereas patients with intractable typical or atypical absence seizures may have a response to valproic acid combined with ethosuximide.[56] It may be counterproductive to introduce a sedative drug such as phenobarbital or primidone, because if the drug is ineffective, its subsequent withdrawal will probably decrease the control of seizures. The addition of one of the newer drugs — lamotrigine, gabapentin, vigabatrin, clobazam, oxcarbazepine, or felbamate — may be more appropriate.

The patient and the doctor may have to accept the persistence of some seizures, despite therapy with multiple drugs. Many patients receive treatment with three or more antiepileptic drugs, although few are made free of seizures by this approach. The likelihood of central nervous system and other toxic effects increases with the number of antiepileptic drugs prescribed. It is important to balance the adequacy of seizure control with the quality of life. Little is lost by gradually reducing the number of drugs and simplifying the dose schedules, and paradoxically, this approach often reduces the frequency of seizures.[57] In a few patients the control of seizures may dramatically deteriorate or tonic–clonic seizures may occur, but a slow reduction in the dose minimizes this possibility. Therapy that results in fewer severe episodes, abolishes tonic–clonic seizures, prevents falls, and decreases automatism is acceptable in some patients with intractable epilepsy. Other options include surgery and a trial of an experimental antiepileptic drug.

Drug Monitoring

Athough measuring plasma drug concentrations can be helpful in determining the optimal dose of an antiepileptic drug in some patients,[58] it is important to treat the patient and not the drug concentration.[59] The therapeutic or target range should be regarded only as an approximation, since it is based on data from only a few patients. Some patients have no seizures when their plasma drug concentrations are low,[60] whereas others require concentrations above the target range to be free of seizures.[61] Nevertheless, appropriate use of plasma drug monitoring, particularly on site at an epilepsy clinic, can be beneficial.[62] In the case of a patient with newly diagnosed epilepsy, who may have infrequent seizures, it makes sense to ensure that the drug concentration is within the appropriate target range. Monitoring is also useful in encouraging compliance, can be helpful in the case of a breakthrough seizure in a patient in whom sei-

zures are otherwise well controlled, and can help the clinician distinguish between too much and too little medication.

Drug Treatment during Pregnancy

In most women treated for epilepsy, seizures remain well controlled during pregnancy; such women have uneventful pregnancies and deliver healthy babies.[63] During pregnancy, metabolic and excretory processes change, however, so that the plasma concentrations of some antiepileptic drugs, particularly phenytoin, can fall.[64] It is important to be alert to this possibility, and pregnant women with epilepsy should therefore be seen more often than those without epilepsy.

There is a small increase in the incidence of serious fetal malformations in the offspring of epileptic women: 3 percent, as compared with 2 percent in the general population.[65] The risk increases with the number of antiepileptic drugs: 3 percent with one drug (which is similar to the incidence in the offspring of women with untreated epilepsy), 5 percent with two, 10 percent with three, and over 20 percent with four.[66] A syndrome consisting of facial dimorphism, cleft lip and palate, cardiac defects, digital hypoplasia, and nail dysplasia has been identified. Initially ascribed to phenytoin (fetal hydantoin syndrome), these malformations are now known to occur with several antiepileptic drugs, including carbamazepine and valproic acid.[67]

Valproic acid and carbamazepine are associated with a higher incidence of neural-tube defects than that in the general population — approximately 1 to 2 percent and 0.5 to 1 percent, respectively.[68,69] In an attempt to prevent such defects, folic acid should be given both before and after conception. There are, however, no data to support the efficacy of this approach in women with epilepsy. Nevertheless, the current recommendations are 5 mg of folic acid per day for women who have had a child with a neural-tube defect and 0.4 mg daily for all other women planning a pregnancy.[70] It seems sensible to recommend the 5-mg dose for women being treated with valproic acid or carbamazepine.

Enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, phenobarbital, and primidone) can cause a transient and reversible deficiency in vitamin K–dependent clotting factors in the neonate, with an increased risk of intracerebral hemorrhage.[71] Women receiving one or more of these drugs should be treated with 20 mg of vitamin K_1 daily during the last few weeks of pregnancy, and their babies should receive a single intramuscular dose of 1 mg of vitamin K_1 immediately after birth.

Discontinuing Therapy

In more than 60 percent of patients who remain free of seizures, the medication can eventually be withdrawn successfully.[72-75] Some physicians wait for two years, and others for five.[76] Most advise a slow reduction in the dose of each drug during a period of two to six months.[77] Children who have benign epilepsy with rolandic spikes or benign familial neonatal convulsions usually do well after drug withdrawal, whereas those with juvenile myoclonic epilepsy often have relapses.[74] Patients with idiopathic generalized seizures, whether absence or tonic–clonic seizures, are least likely to have a recurrence after control has been achieved and medication withdrawn. Even complex partial seizures can disappear, however, after a long period of control. The patients with the highest probability of remaining free of seizures after the medication has been discontinued are those who have had no seizures for a long period, those who had few seizures before control was achieved, and those with a normal neurologic examination and no structural brain lesion.[78]

Table 6. Important Side Effects of Antiepileptic Drugs.

Drug	Side Effect	
	dose-related	idiosyncratic
Carbamazepine	Diplopia Dizziness Headache Nausea Drowsiness Neutropenia Hyponatremia	Morbilliform rash Agranulocytosis Aplastic anemia Hepatotoxic effects Stevens–Johnson syndrome Teratogenicity
Phenytoin	Nystagmus Ataxia Nausea Vomiting Gum hypertrophy Depression Drowsiness Paradoxical increase in seizures Megaloblastic anemia	Acne Coarse facies Hirsutism Blood dyscrasias Lupus-like syndrome Rash Stevens–Johnson syndrome Dupuytren's contracture Hepatotoxic effects Teratogenicity
Valproic acid	Tremor Weight gain Dyspepsia Nausea Vomiting Alopecia Peripheral edema	Acute pancreatitis Hepatotoxic effects Thrombocytopenia Encephalopathy Teratogenicity
Phenobarbital	Fatigue Listlessness Depression Insomnia (in children) Distractability (in children) Hyperkinesia (in children) Irritability (in children)	Maculopapular rash Exfoliation Toxic epidermal necrolysis Hepatotoxic effects Arthritic changes Dupuytren's contracture Teratogenicity
Primidone	Fatigue Listlessness Depression Psychosis Decreased libido Impotence	Rash Agranulocytosis Thrombocytopenia Lupus-like syndrome Teratogenicity
Ethosuximide	Nausea Anorexia Vomiting Agitation Drowsiness Headache Lethargy	Rash Erythema multiforme Stevens–Johnson syndrome Lupus-like syndrome Agranulocytosis Aplastic anemia
Clonazepam	Fatigue Sedation Drowsiness Dizziness Aggression (in children) Hyperkinesia (in children)	Rash Thrombocytopenia

Referral to an Epilepsy Center

Some patients with uncomplicated epilepsy are cared for by family practitioners, internists, or pediatricians.

Since an accurate classification of the seizures and syndrome, with appropriate selection and supervision of medication, is critical for optimal management, however, a neurologist or other specialist in epilepsy should be involved early in the evaluation. Patients with more complicated seizure problems are more appropriately cared for by epileptologists, who can provide additional expertise in diagnosis and treatment.

Patients who continue to have seizures that cannot be ascribed to poor compliance with therapy should be referred to an epilepsy center, for several reasons. First, the more seizures a patient has, the more difficult it is to control the epilepsy[79]; that seizures may beget seizures has been hypothesized for more than a century.[80] Second, it may be hard to classify the seizures on the basis of accounts by untrained eyewitnesses. Video electroencephalographic monitoring can result in a definitive diagnosis and classification.[81] In some patients, apparently uncontrolled seizures are really pseudoseizures, which are better treated with psychotherapy. Third, patients with uncontrolled seizures often receive multiple drugs, which may have substantial toxic effects that can be reduced by simplification of the regimen.[82] Fourth, in patients who have not had adequate responses to the standard drugs, there may be an opportunity to try an experimental drug. Finally, appropriate decisions about surgical treatment are best made at a specialized center.[83]

Conclusions

We have provided an overview of the practical management of epilepsy with established antiepileptic drugs. These agents should be prescribed with the following rules in mind. The diagnosis of epilepsy must be sound, and there should be no correctable underlying condition. The patient must be counseled about the implications of the diagnosis, the need for long-term therapy, and the importance of compliance. The choice of drug should be based on proper classification of the type of seizure and epileptic syndrome. Initial doses should be low and increased incrementally to a maintenance dose that controls the seizures without toxic effects; doses should be titrated to the limit of tolerability without concern about the plasma concentration. Monotherapy is the preferred approach for most patients, and a second drug, or even a third, should be substituted for the first before a combination of drugs is contemplated. Patients should be referred to an epilepsy center when seizures persist despite treatment with first-line antiepileptic drugs, and surgery should be considered for patients with drug-resistant partial seizures or generalized seizures with multiple falls. Good communication with the patient and family, combined with simple, clear, and sympathetic explanations of the plan of action and potential pitfalls, is essential. In most cases, treatment is effective, and people with epilepsy can usually lead healthy and productive lives.

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