CLINICAL PRACTICE

Initial Management of Epilepsy

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 29-year-old woman presents for evaluation. The previous evening, her husband, who was in the next room, heard unusual sounds and found her lying on the bed looking dazed. She was confused for a few minutes but quickly returned to normal. On questioning, she recalls an unwitnessed event about 1 month previously; at that time, she awoke feeling mildly confused, had sore muscles, and discovered she had bitten her tongue. How should she be evaluated and treated?

THE CLINICAL PROBLEM

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Epilepsy, which is defined as two or more seizures that are not provoked by other illnesses or circumstances, affects about 45 million people worldwide. In the United States, the prevalence of epilepsy is approximately 6 to 8 per 1000 population, and the incidence is approximately 26 to 40 per 100,000 person-years, with higher rates among infants and persons older than 60 years of age.[1-3] Approximately 70% of adults with new-onset epilepsy have partial (focal) seizures.[3] In the majority of cases (62%), the cause is unknown. Stroke (9.0%), head trauma (9.0%), alcohol (6.0%), neurodegenerative disease (4.0%), static encephalopathy (3.5%), brain tumors (3.0%), and infection (2.0%) account for most remaining cases.[4] Although cerebrovascular causes are more common in the elderly, the cause is still unknown in 25 to 40% of patients who are 65 years of age or older.[5]

STRATEGIES AND EVIDENCE

DIAGNOSIS

The transient occurrence of altered awareness, abnormal behavior, or involuntary movements suggests a diagnosis of epilepsy. Because epileptic seizures are rarely observed by a physician, the diagnosis is typically based on historical information supplemented by selected tests. The first step is to answer the question of whether the event was a seizure. The second is to determine whether the patient has epilepsy.

A careful history is the single most important element in diagnosis, with a focus on details of the episode and whether there is any history of previous spells that may point to a diagnosis of epilepsy. When patients have limited or no recall of events, witnesses should be queried about details of the episode. The differential diagnosis varies according to the patient's age and symptoms (Table 1).

Seizures are common in metabolic (e.g., uremia, hypoglycemia, hyperglycemia, and hepatic failure), toxic (e.g., drug overdose or withdrawal), and infectious (e.g., meningitis and encephalitis) conditions.[6] Seizures that occur in patients with these conditions do not necessarily confer a diagnosis of epilepsy. Although antiepileptic drugs are sometimes necessary to suppress seizures in the short term in these conditions, medications generally do not need to be continued after the patient has recovered.

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Table 1. Conditions That Can Mimic Epileptic Seizures.

Diagnosis	Important Clinical Features
Hyperventilation	Anxiety and overbreathing evident; often perioral cyanosis, hand paresthesias, and carpopedal spasm are present; environmental trigger may be evident
Migraine	Slow progression of neurologic symptoms; visual symptoms prominent; basilar migraine has unusual features, including confusion, stupor, bilateral blindness; headache may be minimal or absent
Panic attack	Abrupt onset with intense feeling of dread or fear; often sense of impending death or inability to breathe; prominent autonomic features (e.g., tachycardia, sweating, nausea); lasts longer (5–30 min) than typical seizure; no loss of consciousness
Psychogenic seizures	Psychiatric history; patient usually motionless with eyes closed at onset; fluttering eye movements and forceful eye closure common; out-of-phase, thrashing limb movements and pelvic thrusting common; urinary incontinence unusual; refractory to treatment
Syncope	Precipitating circumstances usually identifiable; prodrome of wooziness but no aura or unilateral symptoms; loss of consciousness brief (<20 sec), with rapid return to normal; a few muscle jerks ("convulsive syncope") can occur at end because of hypoxia
Transient global amnesia	Isolated amnesic syndrome; prolonged duration (several hours); no alteration of consciousness; no confusion, weakness, or aphasia; persistent memory gap during period of attack; recurrence unusual
Transient ischemic attack	Sudden onset without progression of symptoms; variable symptoms related to brain and vascular anatomy; negative features (e.g., weakness, loss of sensation, aphasia) predominate

EVALUATION

The neurologic examination is normal in most patients with epilepsy. Findings occasionally point to an underlying pathologic condition in the brain or a specific disorder such as skin abnormalities in neurocutaneous syndromes. According to joint recommendations of the American Academy of Neurology and the American Epilepsy Society, patients with an unprovoked first seizure[7] should undergo electroencephalography (EEG), computed tomographic (CT) scanning or magnetic resonance imaging (MRI) of the head, and selected blood tests according to the clinical circumstances. Epileptiform EEG patterns such as spikes and sharp waves can assist in the diagnosis and in classifying seizures as being either focal or generalized. However, neither a normal EEG nor interictal abnormalities alone refute or confirm a diagnosis of epilepsy. EEGs are abnormal in about 50% of patients presenting with a first seizure, and they show epileptiform discharges in only about half of these patients.[7] The incidence of abnormalities increases when EEGs are repeated or performed after the patient has undergone sleep deprivation.[8] Video EEG monitoring is necessary if there is concern about nonepileptic events (Table 1).

MRI of the brain is more sensitive than CT in identifying structural lesions causally related to epilepsy.[9] CT, however, is appropriate for emergency situations. Among patients in whom epilepsy has been newly diagnosed, CT of the head is abnormal in 34 to 56%, and cranial CT findings affect management in 9 to 17%.[10]

Routine blood tests rarely inform the diagnosis in otherwise healthy patients. However, a complete blood count, liver-function tests, and measurement of electrolyte levels are useful before antiepileptic drug treatment is initiated, since dosage adjustment may be necessary if hepatic or renal function is abnormal. Albumin levels should be measured before administering highly protein-bound drugs such as phenytoin and valproate, since the fraction of unbound (active) drug is higher in patients with hypoalbuminemia. In adolescents and adults with unexplained generalized seizures, screening for substance abuse should be considered.

A diagnosis of epilepsy can have a considerable effect on the patient's mood, interpersonal relationships, employability, social functioning, quality of life, and ability to drive. Early and repeated discussions of these issues are suggested. Patients should be discouraged from participating in activities for which a history of seizures increases the risk of injury or death; these activities include driving, operating high-risk power equipment,

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Table 2. Initiation of Antiepileptic Drugs as Initial Monotherapy in the Absence of Special Considerations.

Drug	Starting Daily Dose and Titration	Typical Initial Target Dose	Blood Level	Common Side Effects	Serious Side Effects	Other Considerations
		mg/day	*μg/ml*			
Carbamazepine (Tegretol, Carbatrol, Tegretol XR)	200 mg; increase daily dose by 200 mg every 3 days	400–600	4–12	Dizziness, diplopia, blurred vision, ataxia, sedation, weight gain, nausea, benign leukopenia*	Agranulocytosis (in approximately 1/200,000 patients), aplastic anemia (in 1/500,000 patients) hepatic failure (very rare), rash (in approximately 10% of patients), Stevens–Johnson syndrome (rare),† hyponatremia (in 1.8–40.0% of patients)	Monitor sodium, liver-function tests, complete blood count; induces its own metabolism
Gabapentin (Neurontin)	300–600 mg; increase daily dose by 300–600 mg each wk‡	900	12–20	Sedation, fatigue, dizziness, mild weight gain, ataxia, behavioral effects (in children)	None known	Gastrointestinal absorption dose-dependent, reducing bioavailability at doses >1200 mg/day
Lamotrigine (Lamictal, Lamictal XR)	25 mg; initial monotherapy: 25 mg/day for 2 wk, then 50 mg/day for 2 wk, followed by increases in the daily dose of 25–50 mg each wk	100–200	3–14	Dizziness, blurred vision, insomnia, headache	Rash, Stevens–Johnson syndrome (in 1–3/1000 patients); hypersensitivity, multiorgan failure, hepatic failure (all rare)	
Levetiracetam (Keppra, Keppra IV)	250–500 mg; increase daily dose by 250–500 mg each wk‡§	1000–2000	10–40	Fatigue, dizziness, irritability, anxiety, asthenia	Psychosis (rare)	
Oxcarbazepine (Trileptal)	300–600 mg; increase daily dose by 300–600 mg each wk	900–1200	3–40 (10-monohydroxy metabolite)	Fatigue, dizziness, ataxia, diplopia, nausea, vomiting, headache	Rash; Stevens–Johnson syndrome or toxic epidermal necrolysis (0.5–6.0 cases per million patients), hyponatremia (serum sodium level, <125 mmol per liter) (in 2.5% of patients), anaphylaxis (rare)	10-monohydroxy metabolite is active component
Phenytoin (Dilantin, Phenytek)	If initiated without titration, 3–5 mg/kg; may be initiated with a loading dose‡§	200–300	10–20	Fatigue, dizziness, ataxia, diplopia, nausea, vomiting, confusion	Blood dyscrasias (rare), conduction block, pseudolymphoma, rash, Stevens–Johnson syndrome, or toxic epidermal necrolysis (in 2–4/10,000 patients), hepatic failure (rare), lupus-like syndrome	Nonlinear kinetics may lead to rapid increases in serum concentration with toxic effects after small changes in dose; gum hypertrophy, hirsutism may occur with long-term use; risk of osteopenia

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Phenobarbital (generic only)	30 mg; increase daily dose by 30 mg every 2 wk	60–120	15–45	Fatigue, dizziness, ataxia, diplopia, nausea, vomiting, confusion, depression, hyperactivity (in children)	Generally rare; blood dyscrasias, hepatic failure, rash, Stevens–Johnson syndrome or toxic epidermal necrolysis, arthritis	
Pregabalin (Lyrica)	75–150 mg; increase daily dose by 75–150 mg each wk‡	150–300	Not established	Fatigue, dizziness, ataxia, diplopia, weight gain, edema	None reported	Schedule V controlled substance
Tiagabine (Gabitril)	4 mg; increase daily dose by 4 mg each wk	16–36	Not useful	Fatigue, dizziness, ataxia, somnolence, nervousness, weakness	Spike-wave status epilepticus	
Topiramate (Topamax)	25–50 mg; increase daily dose by 25–50 mg each wk	100–200	5–25	Drowsiness, ataxia, word-finding difficulty and slowed speech, difficulty concentrating, anorexia, weight loss, paresthesias, metabolic acidosis, oligohydrosis (mostly in children)	Significant metabolic acidosis (in 3% of patients), renal calculi (in 1.5% of patients), acute glaucoma (rare), heatstroke	
Valproate, valproic acid (Depakene, Depacon), divalproex sodium (Depakote, Depakote ER)	250–500 mg, or 10–15 mg/kg orally once a day; increase daily dose by 250–500 mg each wk§	750–2000	40–100	Drowsiness, ataxia, weight gain, nausea, vomiting, thrombocytopenia, tremor, hair loss	Hepatic failure (in 1/20,000 patients, higher rate among children and with polytherapy), hyperammonemia, aplastic anemia (rare), pancreatitis (in 1/3000 patients), thrombocytopenia	
Zonisamide (Zonegran)	50 mg; increase daily dose by 50 mg each wk	100–200	10–40	Drowsiness, ataxia, difficulty concentrating, irritability, anorexia, weight loss, nausea, vomiting, headache, oligohydrosis (mostly in children)	Aplastic anemia, renal calculi (in 0.2–4.0% of patients), rash (in 1–2% of patients), Stevens–Johnson syndrome or toxic epidermal necrolysis (rare), heatstroke (rare)	

* There is usually no need for intervention unless the neutrophil count is below 1000 cells per cubic millimeter.
† HLA-B*1502 testing is now recommended in patients of Asian descent, since this haplotype is associated with a higher risk of Stevens–Johnson syndrome.[26]
‡ This drug can be initiated at a therapeutic dose.
§ This drug can be administered intravenously.

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Table 3. Factors Affecting the Choice of Antiepileptic Drugs in Specific Patient Populations.*

Drug	Patient Population					Other Considerations
	Women†	Patients with Coexisting Medical Conditions	Elderly Patients	Patients with Generalized (Myoclonic or Absence) Seizures	Patients with Developmental Delay or Symptomatic Generalized Epilepsy	
Carbamazepine	OCP interaction; increased risk of fetal anticonvulsant syndrome in offspring if taken during pregnancy	Enzyme induction may lead to interactions with other medications; caution in patients with hepatic disease, blood dyscrasias, and arrhythmias, in patients at risk for hyponatremia, and in Asian patients (increased risk of rash); reduces T_4 and free T_4 levels	Increased sedation and hyponatremia	May aggravate generalized seizures	May aggravate myoclonus, typical absence seizures, atypical absence seizures	Mild weight gain; genotyping suggested in patients of Asian descent because of increased risk of rash with HLA-B*1502 allele; relatively inexpensive
Gabapentin		Reduce dose in patients with impaired renal function	Reduced dose required	May aggravate generalized seizures	May aggravate myoclonus	Mild weight gain
Lamotrigine	Levels of lamotrigine decrease in pregnancy, with concomitant OCP use; reports of cleft lip and palate in babies	Caution in patients with known hypersensitivity to antiepileptic drugs; dose reduction may be necessary in hepatic disease		May aggravate myoclonus	May aggravate myoclonus	
Levetiracetam		Reduce dose in patients with renal impairment	Reduced dose required			Behavioral issues; caution in patients with known psychiatric disorder
Oxcarbazepine	OCP interaction	Caution in patients with carbamazepine hypersensitivity and in patients at risk for hyponatremia; reduces T_4 and free T_4 levels	Risk of hyponatremia	May aggravate generalized seizures	May aggravate myoclonus, atypical absence seizures	
Phenytoin	OCP interaction; increased risk of fetal anticonvulsant syndrome (including hypertelorism, epicanthal folds, digital hyperplasia, and higher risk of major malformations) in offspring if taken during pregnancy	Enzyme induction may lead to interactions with other medications; caution in patients with liver disease; reduces T_4 and free T_4 levels; may worsen heart block or arrhythmia; may mask symptoms of hypoglycemia in diabetes; may cause hypotension	Not always well tolerated; more likely to lead to nonlinear kinetics‡			Reduces bone density; increased risk of gingival hyperplasia, hirsutism, coarsened facial features, lymphadenopathy; relatively inexpensive

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Phenobarbital	OCP interaction; possible teratogen	Enzyme induction may lead to interactions with other medications; caution in patients with liver disease; reduce dose in patients with renal impairment	Risk of cognitive dysfunction		Increased risk of behavioral issues	May cause exacerbation of seizures when withdrawn, hyperactivity in children; least expensive antiepileptic drug
Pregabalin		Reduce dose in patients with renal impairment	Reduced dose required	May aggravate myoclonus		Weight gain, peripheral edema
Tiagabine				May aggravate myoclonus	May aggravate myoclonus, atypical absence seizures	
Topiramate	OCP interaction at doses >200 mg	Renal calculi, may cause metabolic acidosis; reduce dose in patients with renal impairment	Reduced dose may be required			Weight loss; rarely oligohydrosis or hyperthermia
Valproate, valproic acid, divalproex sodium	Possible PCO syndrome, teratogenicity, and decreased intellectual function in offspring if taken during pregnancy	Enzyme inhibition may lead to possible interactions with other medications; caution in patients with hepatic dysfunction and in patients at risk for bleeding; can cause pancreatitis				Weight gain, alopecia
Zonisamide		Renal calculi; reduce dose in patients with renal impairment; may need to reduce dose in hepatic impairment	May need to reduce dose			Weight loss; rarely oligohydrosis or hyperthermia

* Dose-related and idiosyncratic reactions are listed only if certain populations are at increased risk for these reactions. OCP denotes oral contraceptive pill or patch, PCO polycystic ovary syndrome, and T_4 thyroxine.
† Limited data are available on the use of newer agents (e.g., gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide) during pregnancy.
‡ When the phenytoin metabolic pathway is saturated, metabolism switches to zero-order kinetics and clearance is substantially reduced; this can lead to toxic levels of the drug.

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working at heights, and swimming or bathing alone. In most states, patients who are not seizure-free are prohibited from driving; the required duration of time without seizures varies across states and ranges from 3 months to 1 year.[11]

As many as 55% of patients with uncontrolled seizures are depressed.[12,13] Even patients with well-controlled seizures have rates of depression that are higher than rates among the general population, and suicide rates are tripled, with the highest rates in the 6 months after diagnosis.[14-16] Patients should be observed for signs of depression and queried specifically about their mood, with attention to the potential need for psychiatric referral and treatment. A simple screening tool developed specifically for use in people with epilepsy may facilitate prompt recognition of major depression.[17,18]

A recent Food and Drug Administration advisory indicated an increased risk of suicidal thoughts among patients who were in the treatment group in add-on studies of new antiepileptic drugs.[19] Over the 2 to 6 months of treatment in the various studies, the absolute risk was 0.43% among patients receiving active treatment as compared with 0.22% among patients in the placebo group. These findings provide support for the assessment of mood in patients who are starting antiepileptic drug therapy.

PHARMACOLOGIC THERAPY

Opinion remains divided about treating patients who have had only a single seizure, since only about 25% of patients will have a recurrence within 2 years in the absence of factors that predict a high probability of recurrence (e.g., epileptiform activity detected on an EEG or a known cause such as remote major head trauma).[20] Even with one or more risk factors, the recurrence rate at 2 years is no more than 40%. Furthermore, although randomized trials have shown that treatment reduces the risk of seizure recurrence by 30 to 60%, the likelihood of being seizure-free at 3 to 5 years after a first or second seizure was similar whether treatment was started after the first or second seizure or deferred initially and started only if a seizure recurred.[21] Treatment is almost always justified when a diagnosis of epilepsy has been made.

In the past two decades, nine new antiepileptic drugs have been marketed, making the choice of initial therapy complex. Antiepileptic drugs are classified as being either broad-spectrum or narrow-spectrum drugs with regard to efficacy against different seizure types and epilepsy syndromes. Broad-spectrum antiepileptic drugs are particularly useful because they are reasonable initial choices in most adult patients, regardless of the type of seizure or syndrome. These drugs include valproate, lamotrigine, topiramate, and levetiracetam (the efficacy of which [in generalized seizures] is supported by randomized, controlled trials), and zonisamide (the efficacy of which [in generalized seizures] is based on open studies and clinical experience). In contrast, narrow-spectrum drugs, which include carbamazepine, phenytoin, gabapentin, tiagabine, oxcarbazepine, and pregabalin, should be restricted to patients who have localization-related (focal) epilepsy with partial and secondarily generalized seizures.[22] These drugs are less effective than broad-spectrum agents in the idiopathic generalized epilepsy syndromes (e.g., juvenile myoclonic epilepsy and childhood absence epilepsy), and they may even exacerbate some seizure types in these patients.[23] About half of patients in whom epilepsy is newly diagnosed become seizure-free while receiving the first antiepileptic drug. Failure of the first antiepileptic drug for reasons other than tolerability increases the likelihood of nonresponse to other drugs, but nearly two thirds of patients become seizure-free after receiving the second or third drug.[24]

Head-to-head trials suggest similar efficacy among the various antiepileptic drugs against partial seizures.[22] However, a recent large, pragmatic, randomized, controlled trial involving patients with generalized epilepsy showed valproic acid to be more effective than lamotrigine and topiramate. Lamotrigine had almost twice the failure rate because of inadequate seizure control, whereas topiramate was similarly effective in controlling seizures but had a higher failure rate caused by discontinuation because of side effects.[25]

The selection of medication should be informed by patient characteristics, including sex, age, and coexisting conditions that affect the likelihood of adverse events. Table 2 provides useful information regarding the initiation of antiepileptic drugs. A common practice in patients who present with a first seizure has been to provide a loading dose of phenytoin in the emergency department. However, clinical trials in newly diagnosed epilepsy have not shown any advantage associated with phenytoin,[27] and it is generally preferable to initiate whichever antiepileptic drug is considered to

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be most appropriate with regard to other patient characteristics. Table 3 lists considerations relevant to selecting initial therapy in particular patient populations.

Adverse Effects

Table 2 lists dose-related, idiosyncratic, and long-term adverse effects of antiepileptic drugs. Loss of bone density may occur during treatment with phenytoin and possibly with other hepatic enzyme–inducing antiepileptic drugs such as carbamazepine and phenobarbital.[28,29] Both men and women who take enzyme-inducing drugs should receive supplemental vitamin D (up to 2000 IU daily) and calcium (up to 1200 mg per day), and they should have periodic bone-density measurement.[29]

Choice of Antiepileptic Drugs in Women

Antiepileptic drugs, and especially valproate, have been associated with reproductive endocrine disorders, most notably features of polycystic ovary syndrome (e.g., irregular menstrual cycles, weight gain, and hirsutism).[30,31] This association appears to be related at least in part to the epilepsy itself,[32,33] but in the majority of women, medication seems to play the major role.[34,35] Observational studies have shown clinically important associations between the use of valproate, alone or in combination with other drugs, and the development of polycystic ovaries, anovulatory cycles, and hyperandrogenism.[34,36,37]

Hepatic enzyme–inducing antiepileptic drugs such as phenytoin, carbamazepine, and phenobarbital, as well as topiramate and oxcarbazepine, increase the clearance of oral contraceptive pills. Thus, women taking these drugs who use oral contraceptive pills are advised to use preparations containing at least 50 μg of ethinyl estradiol in order to reduce the chance of pregnancy.[38] However, the contraceptive efficacy of higher-dose oral contraceptive pills has not been well studied, and alternative methods (e.g., barrier contraception) should be discussed. The dosage of lamotrigine requires adjustment when oral contraceptive pills are started or discontinued, because oral contraceptives enhance the clearance of lamotrigine.[38] Serum concentrations of lamotrigine should be followed in this setting and in pregnancy,[38] which increases the clearance of many antiepileptic drugs, but particularly that of lamotrigine.

Babies born to women with epilepsy have an increased rate of malformations; this is believed to be attributable mostly to antiepileptic drugs.[39] Studies of the effect of specific drugs during pregnancy are hampered by confounding factors such as the type and severity of epilepsy and the use of more than one agent in many patients. No antiepileptic drug can be considered to be absolutely safe. Newer drugs are less well studied, but the evidence linking valproate to an increased risk of birth defects is most convincing and sufficient to advise against its use in women of childbearing age unless there is no alternative.[40] The risk of birth defects is likely to be minimized further by treating with monotherapy and drug dosages as low as possible during pregnancy, although the evidence to support these recommendations is limited. Retrospective analyses of school-age children have suggested associations between intrauterine exposure to valproate (but not other antiepileptic drugs) and lower IQ scores and developmental delay[41,42]; this finding warrants confirmation in prospective studies.

Concurrent Medical Conditions

Some patients — particularly many elderly patients — may be poor candidates for some antiepileptic drugs because of coexisting conditions or the use of medications with which a given antiepileptic drug may interact.

In patients with hepatic dysfunction, dosing adjustments of drugs metabolized by the liver may be necessary, although their use is not necessarily contraindicated; valproate, however, should be avoided, since it can increase ammonia levels. Many antiepileptic drugs (particularly valproate, phenytoin, phenobarbital, and carbamazepine) can cause elevations in hepatic enzyme levels, particularly alanine aminotransferase and γ-glutamyltransferase.[43] Stable mild elevations (even up to two times the normal range) are not a substantive concern, but they may complicate monitoring of patients with underlying hepatic disease. A history of renal calculi is a relative contraindication to the use of topiramate and zonisamide, which can predispose to stone formation.[44] Both carbamazepine and oxcarbazepine can cause hyponatremia and should generally be avoided in patients with preexisting hyponatremia or risk factors for hyponatremia (e.g., older age, history of excess water intake, renal failure, or concurrent use of other medications associated with hyponatremia).[45]

Levels of drugs metabolized by hepatic mi-

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Table 4. Common Drugs with Either Increased or Reduced Clearance in the Presence of Antiepileptic Drugs.*

Type of Medication	Increased Clearance (and Need for Higher Doses) with Phenytoin, Phenobarbital, Carbamazepine	Decreased Clearance (and Need for Lower Doses) with Valproic Acid
Cardiac	Mexiletine, quinidine, amiodarone, propranolol, metoprolol, nifedipine, felodipine, nimodipine, digoxin, lovastatin, simvastatin, dicoumarol, warfarin	Nimodipine
Psychiatric	Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, citalopram, paroxetine, buproprion, haloperidol, chlorpromazine, clozapine, olanzapine, risperidone, quetiapine	Amitriptyline, nortriptyline, clomipramine, paroxetine
Antineoplastic	Cyclophosphamide, busulfan, etoposide, methotrexate, teniposide, some vinca alkaloids	
Antiinfective	Praziquantel, albendazole, doxycycline, nevirapine, efavirenz, delavirdine, indinavir, ritonavir, saquinavir	Zidovudine, possibly others
Other	Cyclosporine, tacrolimus, diazepam, alprazolam, prednisone, oral contraceptive pills, theophylline, methadone	Lorazepam, diazepam

* Data are from Patsalos and Perucca.[46] This list is not comprehensive.

crosomal enzymes (e.g., cytochrome P-450 and glucuronyl transferases) can be altered considerably by concurrent antiepileptic drug use (Table 4). Enzyme-inducing antiepileptic drugs should be avoided, whenever possible, in patients receiving antiretroviral therapy for human immunodeficiency virus infection, in organ-transplant recipients, and in patients with cancer being treated with chemotherapy.

Other medical conditions may also influence the choice of antiepileptic drugs. Carbamazepine can cause partial or complete heart block and aggravate sick sinus syndrome.[47] Carbamazepine may reduce the white-cell count and should probably be avoided in patients with blood dyscrasias, because a change in the white-cell count may be difficult to interpret. Valproate causes a dose-related thrombocytopenia in up to 17% of patients and should be avoided in patients who are at risk for bleeding.[48,49]

Carbamazepine and gabapentin are associated with modest weight gain (5 to 10 lb [2.3 to 4.5 kg]), and valproate and pregabalin are associated with more substantial weight gain (10 to 50 lb [4.5 to 23.0 kg]) in about one third of patients. These drugs should be avoided, if possible, in patients with diabetes or eating disorders. Felbamate, topiramate, and zonisamide can result in variable weight loss.[50,51] Weight should be recorded before starting antiepileptic drugs and at follow-up visits.

MONITORING

Routine follow-up EEG is not usually indicated, but reassessment can be useful when deciding whether to discontinue antiepileptic drugs, since patients with abnormal EEGs have a modestly higher risk of recurrence.[52] There is controversy about how often to monitor levels of antiepileptic drugs and perform routine laboratory tests (e.g., complete blood count, measurement of electrolyte levels, and liver-function tests).[53] With older antiepileptic drugs (e.g., phenytoin, carbamazepine, valproate, and phenobarbital), yearly monitoring is sufficient in stable patients in whom more frequent monitoring in the first 6 to 12 months after treatment initiation has been normal. Table 2 summarizes recommendations for the monitoring of newer antiepileptic drugs. The target-dose range (listed in Table 2) corresponds to the average blood levels required for tolerability and seizure control. Many patients do well with levels above or below those values; thus, dosages should be adjusted primarily on the basis of seizure control and side effects.[53]

AREAS OF UNCERTAINTY

There is considerable uncertainty as to when antiepileptic drugs can be discontinued. In various studies, the incidence of seizure recurrence after withdrawal of the drug after a 2-year seizure-free period ranges from 12 to 66%.[54,55] Risk factors

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for relapse include the onset of epilepsy in adolescence, partial seizures, abnormal EEG, and specific epilepsy syndromes. The decision to withdraw antiepileptic drugs depends on individual circumstance and patient preference.

GUIDELINES FROM PROFESSIONAL SOCIETIES

The American Academy of Neurology, the American Epilepsy Society, and the International League against Epilepsy have issued guidelines for the selection of pharmacologic therapy in patients with newly diagnosed epilepsy.[22,56] As described above, the American Academy of Neurology has also released guidelines on the evaluation of patients with an unprovoked first seizure and neuroimaging of patients with a seizure who are seen in the emergency department.[7,10] The recommendations in this article are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has had two probable seizures, one witnessed and the other suggested by history, and it is therefore appropriate to initiate antiepileptic drug therapy. Evaluation would include a thorough neurologic examination, EEG, and brain MRI, but treatment would not be dependent on abnormal findings. If the EEG and MRI are normal, there is insufficient information to classify the seizures definitively as being partial or generalized, so a broad-spectrum antiepileptic drug is preferable. If the patient uses, or plans to use, an oral contraceptive pill, it would be preferable to avoid antiepileptic drugs that will increase the clearance of oral contraceptive pills (see above); oral contraceptive pills with a higher estrogen content, which are commonly recommended in this setting, may carry increased health risks. Valproate should also be avoided because of the risk of teratogenicity. We would consider lamotrigine or levetiracetam to be preferred options for initial treatment in this patient; as always, this recommendation should be predicated on individual patient characteristics.

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An audio version of this article is available at www.nejm.org.

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