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.

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,

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

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
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.

Schedule V controlled substance

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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