CLINICAL PRACTICE

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# Initial Management of Seizure in Adults

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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 author's clinical recommendations.*

**An 18-year-old woman is brought to the emergency department after having had a seizure. She was up late with friends the night before and drank some alcohol. Shortly after waking this morning, she collapsed without warning, injuring her face. Her boyfriend witnessed her having a generalized tonic–clonic seizure with cyanosis during which she bit the side of her tongue. Her first memory was waking in the ambulance. She has had no previous seizures; specifically, she has not had any involuntary jerks of the arms and legs on awakening, blank spells, or sensitivity to flashing lights (e.g., sunlight flashing through trees, as seen while riding in a car). How should this patient be further evaluated and treated?**

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N Engl J Med 2021;385:251-63.
DOI: 10.1056/NEJMcp2024526


## THE CLINICAL PROBLEM

The incidence rate of a single unprovoked seizure among adults is 23 to 61 cases per 100,000 person-years.[1] A seizure may substantially affect a person's social interactions, employment, and driving eligibility. After a first unprovoked seizure, the overall risk of recurrence may be as high as 60% (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), and this risk is highest within the first 2 years.[2] Epilepsy affects 0.65% of adults worldwide,[3] and this incidence is highest in developing countries. Epilepsy is diagnosed after two unprovoked seizures that occur more than 24 hours apart or after a single event that occurs in a person who is considered to have a high risk of recurrence (>60% risk in a 10-year period).[4] Abnormal findings on electroencephalography (EEG), an abnormal neurologic status, and a second seizure all increase the probability of seizure recurrence.[5] These three factors allow clinicians to stratify low, medium, and high risks (Table 1) and help in guiding decisions about the initiation of antiseizure medication.

Occasionally, serial seizures or status epilepticus will manifest as a first seizure, and these conditions may be life-threatening. The management of these conditions is described elsewhere.[6]

*An audio version of this article is available at NEJM.org*

## STRATEGIES AND EVIDENCE

### DIAGNOSIS AND EVALUATION

Expert history taking is essential in the diagnosis of an epileptic seizure. Telephoning an eyewitness is often invaluable, and home video recordings of patients with frequent seizures can help in the diagnosis. Table 2 summarizes the main differential diagnoses of a first generalized tonic–clonic seizure and provides information on the history taking, examination, and initial investigations. Careful

**KEY CLINICAL POINTS**

**INITIAL MANAGEMENT OF SEIZURE IN ADULTS**

- The clinical diagnosis of an epileptic seizure requires a detailed history taking and, ideally, an eyewitness account of the seizure.
- Evaluation with 12-lead electrocardiography is essential in a patient who has had a first seizure or an unexplained blackout spell.
- In children and teenagers, interictal electroencephalography, ideally within 24 hours after a first seizure, is particularly important.
- All patients who have had a suspected focal-onset seizure should undergo detailed magnetic resonance imaging of the head.
- Patients who have had an epileptic seizure should be informed about factors that may provoke seizures (e.g., sleep deprivation and alcohol use), the risk of a seizure occurring while driving or engaging in solitary activities, and the risks of harm from further seizures.
- Data from long-term pragmatic trials suggest that the first-line medication for patients with focal-onset seizures is either lamotrigine or levetiracetam, although other reasonable options are available; for patients with generalized-onset seizures, the first choice is sodium valproate, except for women of childbearing potential, in whom the first-line medication is usually levetiracetam.

history taking can usually distinguish the three main causes of transient loss of consciousness: epileptic seizure (provoked or unprovoked), syncope (reflex, orthostatic, or cardiac), and psychogenic nonepileptic seizure (which mimics a seizure but is caused by psychological distress rather than abnormal electrical activity in the brain).

Provoked seizures might follow transient cerebral insults such as alcohol withdrawal, the use of illicit drugs such as cocaine and methamphetamine, and metabolic disturbances (e.g., hypoglycemia or hyponatremia). They also may suggest a structural cause such as hemorrhagic stroke, encephalitis, venous sinus thrombosis, or tumor.

Seizures and epilepsy are classified according to seizure type (generalized, focal, or unknown[8]), epilepsy type, and epilepsy syndrome.[9] Table 3 and Table S1 provide common examples of each.

The presentation of a seizure depends on its site of onset (generalized or focal) and pattern of spread. Seizures can occur at any age and in any situation. In some cases, a lack of warning suggests a generalized onset, although a lack of warning is also compatible with focal-onset seizures, especially in the frontal lobe. In other cases (usually focal-onset seizures), there is a specific but often "indescribable" aura — such as déjà vu, an epigastric "rising" sensation, or tastes or smells — usually followed by transient altered awareness.

A convulsive seizure typically has a tonic (stiffening) phase and then a clonic (convulsing) phase. Together these phases last 1 to 3 minutes, typically while the patient has open eyes, apnea, and cyanosis. Patients awaken many minutes later feeling tired and achy, and they sometimes have a lateral tongue bite.

Physical examination may reveal findings that point to a cause other than seizure or a condition predisposing to seizure. Attention should be paid to the skin (e.g., to detect facial angiofibromas, hypomelanotic macules suggestive of tuberous sclerosis, or scars from self-harm that are often associated with psychogenic nonepileptic seizures), the cardiovascular system (an aortic ejection murmur may indicate cardiac syncope, and postural blood-pressure changes may indicate orthostatic hypotension), and findings on funduscopic examination (e.g., elevated intracranial pressure).

Basic blood tests to measure levels of electrolytes, glucose, calcium, and magnesium may help to identify potential causes of seizure or coexisting conditions. An evaluation with 12-lead electrocardiography (ECG) is indicated in all patients (especially older adults) who have had a first seizure or unexplained blackout spell to look for evidence of previous myocardial infarction because of the risk of ventricular tachycardia or of rare but potentially fatal (and often familial) disorders, including hypertrophic cardiomyopathy and long QT syndromes.[10]

### BRAIN IMAGING

Urgent brain imaging is warranted in patients who present with a first epileptic seizure. Com-

**Table 1. Probability of Another Seizure after a Single Seizure or Early Epilepsy and Recommendations for Use of Antiseizure Medications.***

| Level of Risk and No. of Seizures | Neurologic Disorder or Abnormal EEG | Probability of Another Seizure | | | Usual Recommendation for Antiseizure Medication |
|---|---|---|---|---|---|
| | | By 1 yr | By 3 yr | By 5 yr | |
| Low risk: 1 seizure | Neither | 0.19 | 0.28 | 0.30 | No |
| Medium risk | | | | | |
| 1 Seizure | Either | 0.35 | 0.50 | 0.56 | Consider |
| 2–3 Seizures | Neither | 0.35 | 0.50 | 0.56 | Consider |
| High risk | | | | | |
| 1 seizure | Both | 0.59 | 0.67 | 0.73 | Yes |
| 2–3 seizures | Either | 0.59 | 0.67 | 0.73 | Yes |
| >3 seizures | Neither | 0.59 | 0.67 | 0.73 | Yes |

* Adapted from Kim et al.[5] EEG denotes electroencephalogram.

puted tomography is useful and widely available. However, in most adults with a first seizure (especially a focal-onset seizure) or early epilepsy, detailed magnetic resonance imaging (MRI; ideally 3-T MRI with <3-mm slice thickness on T2-weighted imaging and fluid-attenuated inversion recovery[11]) is warranted to identify more subtle underlying causes such as hippocampal sclerosis, focal cortical dysplasia, or tumor that may be treated surgically.

### ELECTROENCEPHALOGRAPHY

Interictal EEG that is performed in a patient who has had a first seizure is unlikely to capture another seizure, although the procedure may provoke psychogenic nonepileptic seizures. EEG is most informative in patients younger than 25 years of age because these patients are most likely to have subclinical interictal generalized activity that may confirm a generalized seizure tendency and that strongly predicts further seizures (70% positive predictive value).[12,13]

EEG that is performed soon after a patient has had a first seizure identifies more epileptiform abnormalities than later EEG; one study involving 300 consecutive adults and children identified abnormalities in 51% of those who underwent EEG within 24 hours and in 34% of those who underwent EEG later.[14] EEG that is performed in ambulatory or sleep-deprived patients further increases the diagnostic yield in patients in whom an epileptic seizure is likely even though the routine interictal EEG findings are normal.[15] The presence of interictal epileptiform discharges in either of these investigations increases the 1-year risk of seizure recurrence by a factor of 1.5.[16]

## MANAGEMENT

### ANTISEIZURE MEDICATIONS

The medical management of epilepsy predominantly involves seizure suppression with the long-term use of oral medication (Table 4 and Table S2). Antiseizure medication is primarily indicated when the risk of further spontaneous seizures is judged to exceed 60% over the next 10 years.

The aim of management is no seizures and minimal adverse effects of treatment. However, if these goals prove to be impossible, then the priority is complete control of major convulsive seizures, which are potentially dangerous because they may increase the risk of sudden unexpected death in epilepsy (SUDEP) above the estimated absolute risk among patients with epilepsy overall (1.2 cases per 1000 patient-years).[23]

The initiation of long-term use of antiseizure medication is a major decision that is made by the patient and the clinician. This decision requires reasonable certainty of an epilepsy diagnosis; the use of medication for a trial period in patients in whom the diagnosis is uncertain should be avoided.

The Medical Research Council Multicentre Trial for Early Epilepsy and Single Seizures[24] showed that the risk of seizure recurrence was

**Table 2.** Differential Diagnosis of Generalized Tonic–Clonic Seizure in Adults.*

| Variable | Generalized Tonic–Clonic Seizure | Focal to Bilateral Tonic–Clonic Seizure | Frontal-Lobe Seizure | Reflex (Vasovagal) Syncope | Orthostatic Syncope | Cardiac Syncope | Psychogenic Nonepileptic Seizure | Panic Attack | Non-REM Parasomnia† |
|---|---|---|---|---|---|---|---|---|---|
| Typical demographic characteristics | Young (<25 yr); often no seizure history reported (although on direct questioning, patient may describe absences, myoclonus, photosensitivity, or all these symptoms) | Any age; often with previously unrecognized episodes of déjà vu, epigastric "rising" sensation, blank spells with automatism (e.g., lip smacking and picking at clothes), and tongue biting on waking | Any age, although patients are often children (median onset, 14 yr); possible family history of frontal-lobe seizure (autosomal dominant) | Young; often healthy, with history of fainting | Older age, especially in patients with autonomic failure (diabetes or autonomic neuropathy) or use of vasodilator medications | Older age, with vascular risk factors (especially previous myocardial infarction) | Any age; often with coexisting depression, panic disorder, drug or alcohol dependence, self-harm, or adverse childhood events | Any age; possibly with coexisting depression, anxiety, drug or alcohol dependence, self-harm, or adverse childhood events | Young; usually with onset in childhood and remittance in adolescence; often a family history of parasomnia |
| Occurrence in specific situations | Usually occurs within 1 hr after waking | May occur at any time, including during sleep | Usually occurs during sleep | Commonly situational (e.g., may occur in bathroom or restaurant) and often provoked (e.g., while standing, with the sight of blood, after exertion) | May occur with standing after lying down | Rarely situational, occasionally occurs during exertion | Commonly situational, especially when patient is awake and not alone; often occurs with stressful situations, but patient may report no trigger | Commonly occurs in stressful situations | Always occurs during sleep, especially during first third of the night; worse with sleep deprivation, alcohol use, and stress |
| Warning prodrome | Uncommon | Common, occurs with preceding minor seizure (aura) | None; occurs when patient is asleep | Common; preceding nausea is strongly suggestive; occurs in hot environment, with lightheadedness, visual blackout, or both | Common; occurs with lightheadedness, visual blackout, or both | Uncommon | Common; occurs with fear, panic, and altered mental state, or patient may report no warning | Almost invariable; occurs with fear, panic, and altered mental state | None; occurs when patient is asleep |

| Onset and signs | Sudden onset; highly stereotypical: tonic (stiffening) phase, then clonic (convulsing) phase, together lasting 1–3 min, typically with eyes open, apnea, and cyanosis | Gradual or sudden onset; stereotypical: aura or focal seizure may precede convulsion; in tonic phase, head and gaze deviation to the side contralateral to seizure focus, or "sign of four" (one arm extended, the other flexed) | Sudden onset; variable although highly stereotypical within an individual patient (e.g., dramatic presentation with screaming, semipurposeful motor automatism, including running, or asymmetric tonic posturing with kicking and cycling) | Gradual onset; brief loss of consciousness (<1 min), pallor, sometimes limb jerks and posturing | Gradual or sudden onset; brief loss of consciousness (<1 min), pallor, sometimes limb jerks and posturing | Sudden onset; usually brief but occasionally prolonged loss of consciousness, pallor, and sweating; sometimes limb jerks and posturing | Gradual onset; often prolonged (>2 min) with eyes closed, breathing and color maintained, rapid shaking (especially head and arms), back arching; fluctuating severity | Gradual onset; variable duration, with eyes closed, breathing maintained or rapid, and color maintained | Onset during sleep; variable complexity, not highly stereotypical, lasting seconds to 30 min; confusional arousals; sleepwalking with semipurposeful behavior (e.g., dressing or eating) or sleep terrors |
|---|---|---|---|---|---|---|---|---|---|
| Consciousness and responsiveness | Not during episode | Partial during warning (aura) but not during episode | May be at least partially retained | Not during episode | Not during episode | Not during episode | Variable, even within episode; stimulation can terminate episode | Variable; patient may be responsive | Patient poorly responsive during episode |
| Incontinence | Common | Common | Common | Occasional | Occasional | Occasional | Occasional | Rare | Rare |
| Injury | Common, including lateral tongue biting, facial injury, or posterior shoulder dislocation | Common, including lateral tongue biting; warning limits risk of injury | Common, despite retained awareness | Occasional minor, rare tongue biting | Uncommon (with warning) | Common, including tongue biting | Occasional tongue and cheek biting, wrist injury, carpet burn; occasional directed violence | Occasional minor tongue and cheek biting | Uncommon |
| Recovery | Slow; patient is drowsy, confused, and has muscle aches | Slow; patient is drowsy, confused, and has muscle aches | Rapid | Rapid regaining of consciousness, but patient often fatigued | Often rapid, unless patient remains in upright position during episode | Often rapid | Often slow | Usually rapid | Patient typically returns to sleep |

**Table 2. (Continued.)**

| Variable | Generalized Tonic–Clonic Seizure | Focal to Bilateral Tonic–Clonic Seizure | Frontal-Lobe Seizure | Reflex (Vasovagal) Syncope | Orthostatic Syncope | Cardiac Syncope | Psychogenic Nonepileptic Seizure | Panic Attack | Non-REM Parasomnia† |
|---|---|---|---|---|---|---|---|---|---|
| Findings on examination and initial tests | Lateral tongue biting, facial injury; interictal EEG shows spike–polyspike-and-wave patterns; MRI of head normal, indicated particularly for atypical features (including persistence of seizures despite use of antiseizure medication); 12-lead ECG used to exclude propensity for cardiac arrhythmia mimicking seizure | Lateral tongue biting, cranial scars from previous injury or surgery, hemiatrophy (suggesting mild cerebral palsy); MRI of head may show underlying structural cause; interictal EEG may show focal sharp, spike, and slow waves; 12-lead ECG used to exclude propensity for cardiac arrhythmia mimicking seizure | Cranial scars from previous injury or surgery; MRI of head may show underlying structural cause; EEG may show focal sharp, spike, and slow waves or muscle artifact only, even during seizures (deep focus); video may capture typical event if frequent | Low blood pressure; bedside postural blood-pressure reading usually not necessary or helpful; 12-lead ECG used to exclude propensity for cardiac arrhythmia; head-up tilt-table test (if doubt remains after history, examination, and ECG) may show abrupt bradycardia and hypotension after 15–30 min | Bedside blood pressure decreases over a period of a few minutes while patient is in upright position, without compensatory tachycardia; 12-lead ECG used to exclude propensity for cardiac arrhythmia; ambulatory blood-pressure monitoring if doubt remains | Signs of congestive cardiac failure, ejection systolic murmur (aortic stenosis or hypertrophic cardiomyopathy), or both; 12-lead ECG used to identify propensity for cardiac arrhythmia (especially if patient has had previous myocardial infarction); transthoracic echocardiography used to identify underlying structural cardiac cause; consider urgent cardiology referral | Scars from self-harm; carpet burns; video of events if frequent to look for gradual onset, long duration; patient has partial eyes closed, rapid breathing, absence of cyanosis, limb thrashing, back arching; EEG may capture typical event (especially with photic stimulation) with only ictal movement artifact | Patient appears anxious; video of events if frequent to look for gradual onset, long duration; patient has partial awareness, anxious expression, eyes closed, rapid breathing; EEG may capture typical event (especially with photic stimulation) with only ictal movement artifact | Normal examination; video of events used to distinguish from frontal-lobe epilepsy; EEG while patient is asleep may capture typical event |

* ECG denotes electrocardiography, MRI magnetic resonance imaging, and REM rapid eye movement.
† Data are from Derry.[7]

**Table 3. Common Types of Seizures in Adolescents and Adults.***

| Seizure Type | Description and Common Examples |
|---|---|
| Generalized onset | The patient's symptoms or description of the seizure by a witness do not indicate an anatomical localization of the seizure. It is thought to start within and rapidly engage bilaterally distributed cerebral networks. |
| Motor | Myoclonic seizures manifest as involuntary "jumps" of the arms, legs, or head, especially shortly after waking and with sleep deprivation; generalized tonic–clonic seizures typically occur without warning, although they may follow myoclonic or absence seizures and are most likely to occur within 1 hr after waking and with sleep deprivation. |
| Nonmotor | Typical absences manifest as a brief loss of awareness, with an abrupt onset and offset, provoked by hyperventilation, often with eyelid flickering, and ictal 3-Hz generalized spike-and-wave activity on EEG; atypical absences have a less abrupt onset and offset, with an atypical, generalized spike-and-wave activity on EEG that is slower (<2.5 Hz) than that in typical seizures. |
| Focal onset | Most new-onset seizures in adults, including tonic–clonic seizures, are of focal onset. There is clinical evidence of seizure onset localized to one part of the brain, regardless of whether it subsequently involves the remainder of the brain. The site of onset determines the features: temporal lobe (epigastric "rising" sensation, déjà vu, and smell or taste), frontal lobe (features are often sleep-related, with adversive head turn, arm and leg jerking, and speech arrest), occipital lobe (elementary visual hallucinations in the contralateral visual field), parietal lobe (lateralized sensory symptoms, including pain), or insular cortex (laryngeal constriction, dyspnea, and contralateral somatosensory symptoms). |
| Awareness | In focal-onset aware (formerly called simple partial) seizures, awareness of the self or environment is retained; in focal-onset impaired awareness (formerly called complex partial) seizures, awareness of the self or environment is impaired. |
| Motor features | Motor seizures include automatisms (e.g., lip smacking and picking at clothes) and atonic, tonic, clonic, and myoclonic features; nonmotor seizures include autonomic, behavior arrest, cognitive, emotional, and sensory features. |
| Secondary generalization | In focal to bilateral tonic–clonic (formerly called secondarily generalized) seizures, the focal seizure develops into a tonic–clonic seizure. Such seizures often first occur during sleep. |
| Unknown onset | The origin of a seizure is often uncertain, especially after only one seizure. |

* Data are from Fisher et al.[8]

lower in the first 2 years after the first seizure among patients who received immediate initiation of medication (generally carbamazepine or sodium valproate) than among those who received delayed treatment pending a second seizure (32% vs. 39%), but earlier initiation of treatment did not affect longer-term seizure remission. Adverse events were significantly more common with immediate treatment than with delayed treatment (in 39% and 31% of the patients), and quality-of-life measures were similar in the two groups. Therefore, clinicians usually advise withholding medication in patients who have had a single seizure unless the recurrence risk is particularly high.[4] Despite a low estimated risk of recurrence, some patients choose to receive medication because they have had a particularly severe or injurious first seizure or because they live in areas such as the United Kingdom where a second seizure might extend the driving restriction from 6 months to 12 months.

### FACTORS GUIDING MEDICATION CHOICE

The choice of medication should be guided by the type of seizure and epilepsy syndrome (broadly, valproate or levetiracetam is used in patients with generalized-onset seizures and lamotrigine or levetiracetam is used in those with focal-onset seizures) as well as by the effectiveness, adverse-event profile, and pharmacodynamic and pharmacokinetic properties of a given drug. Coexisting conditions must also be considered. For example,

**Table 4. First-Line Antiseizure Medications.**

| Medication and Indication | Mechanism and Pharmacokinetic Profile | Dose in Adults | Adverse Effects | Interactions | Comments |
|---|---|---|---|---|---|
| Lamotrigine (Lamictal) for focal-onset seizures[17,18]; effective for generalized-onset tonic–clonic seizures but may exacerbate myoclonus and absences | Stabilizes voltage-dependent sodium channels; 50% protein-bound; metabolized in liver; half-life of 12–60 hr | Monotherapy: start 25 mg daily (introduce slowly to avoid rash); initial maintenance therapy, 100–200 mg daily, in 1 or 2 doses | Dose-related effects: drowsiness, insomnia, headache, diplopia; idiosyncratic effect: rash (in approximately 3.5% of patients[19]) sometimes severe in children (Stevens–Johnson syndrome), especially when taken with valproate; teratogenicity: dose-related low risk of major malformations and oral clefts | Effect on other agents: increases carbamazepine epoxide (dizziness, diplopia); with higher doses (>300 mg daily), lowers contraceptive pill concentration (uncertain mechanism) but no definite evidence of contraception failure; effect of other agents: valproate inhibits its metabolism, so that only half the usual dose of valproate is necessary; hormonal contraceptives and pregnancy lower its concentration, potentially with breakthrough seizures | Slowly introduced to avoid rash, so therapeutic dose not reached for 4–6 wk, and additional antiseizure medication may be warranted in that time; important interactions with other antiseizure medications (notably valproate or carbamazepine) warrant dose adjustments; data support safety in pregnancy (early concern regarding increased risk of cleft defect not supported by subsequent studies); serum concentration decreases in pregnancy, so consider measuring serum concentration and temporary dose increases to avoid breakthrough seizures |
| Levetiracetam (Keppra, Roweepra, and Spritam) for focal-onset seizures[18,20] or generalized-onset seizures[21]; first-line treatment for focal-onset seizures in selected patients and for generalized-onset seizures in women of childbearing potential | Binds to synaptic vesicle glycoprotein 2A; not protein-bound; not metabolized in liver; excreted by kidneys largely unchanged; half-life of 6–8 hr | Start 250 mg daily; initial maintenance therapy, 1000–2000 mg daily divided into 2 doses | Dose-related effect: fatigue; idiosyncratic effects: irritability, anxiety, and mood changes; teratogenicity: low risk of major malformations | Effect on other agents: no major effects, but monitor for toxic effects (e.g., double vision and dizziness) if added to carbamazepine; effect of other agents: no major effects | Effective for both focal-onset and generalized-onset seizures; therapeutic dose achieved quickly, so widely used for rapid seizure control; no medication interactions, so suitable for patients receiving other medications (e.g., warfarin); data support good safety profile in pregnancy |

| | | | | | |
|---|---|---|---|---|---|
| Sodium valproate, valproic acid (Depakene, Depakote, Epilim, and Stavzor) for generalized-onset seizures (except in women of childbearing potential)[21,22]; also effective for focal-onset seizures but not widely used for this indication | Increases γ-aminobutyric acid concentration (uncertain mechanism); 90% protein-bound; metabolized in liver; half-life of 12–17 hr, but therapeutic effect longer | Start 200–500 mg daily; initial maintenance therapy, 500–1500 mg daily, in 1 or 2 doses | Dose-related effects: gastrointestinal upset, tremor, irritability, poor sleep, confusion; idiosyncratic effects: hair loss, weight gain, polycystic ovaries, hyperammonemia (occult urea-cycle disorders), hepatotoxic effects (especially in children with *POLG1* mutations or the Alpers syndrome [in 1/50,000 children]); high risk of teratogenicity: major malformations, including spina bifida, in up to 10% of infants, neurodevelopmental delay identifiable in up to 40% of children | Effect on other agents: enzyme inhibition increases lamotrigine concentration (care in combination), increases carbamazepine-10,11-epoxide concentration, and increases sedation with alcohol; protein-bound displacement increases free concentration of other medications (e.g., warfarin); effect of other agents: enzyme-inducing medications lower total valproate concentration (e.g., carbamazepine, phenytoin); protein-bound medications (e.g., aspirin) displace and increase free valproate concentration | Highly effective for generalized-onset seizures, but powerful teratogenicity and neurodevelopmental delay severely limit its use in young women; enzyme inhibitor, so use caution with alcohol and other medications metabolized by the liver; contraindicated in patients with some mitochondrial diseases (liver failure may occur in patients with *POLG1* mutations) |

patients with substantial anxiety may prefer lamotrigine over levetiracetam, whereas those with obesity or migraines may choose topiramate, which can suppress appetite and reduce the incidence of headaches. An overriding consideration for women is the effects of medication on potential pregnancy.

Although a detailed discussion of the use of antiseizure medication in women who may become pregnant is beyond the scope of this article, sodium valproate carries high risks in pregnancy. Approximately 10% of babies exposed to sodium valproate in utero have major congenital anomalies,[25] and up to 40% have measurable neurodevelopmental delay.[26] In the European Registry of Antiepileptic Drugs and Pregnancy (EURAP) Study Group prospective study involving 7555 pregnancies,[27] 10.3% of the infants had major congenital malformations after in utero exposure to valproate, 5.5% had these malformations after exposure to carbamazepine, 3.9% after topiramate, 3.0% after oxcarbazepine, 2.9% after lamotrigine, and 2.8% after levetiracetam (as compared with a 2.6% risk among infants who had not been exposed in utero to antiseizure medication[28]). The possible contribution of maternal seizures to the risks of congenital anomalies and neurodevelopmental delay remains unclear.

The EURAP study also showed that major congenital malformations associated with valproate were dose-related and included cardiac defects and hypospadias, each of which was found in 2% of infants with exposure to valproate; cleft lip; gastrointestinal, renal, and neural-tube defects; and polydactyly. Cognitive assessments in 6-year-old children who had had in utero exposure to valproate showed significant dose-related inverse associations with IQ, verbal ability, and nonverbal ability; these effects were not observed in children with in utero exposure to other antiseizure medications.[26] Thus, valproate should generally be avoided in women of childbearing potential; if valproate is used, effective measures should be taken to prevent pregnancy unless the woman is fully informed about the risks. As part of a licensing requirement since 2018 in the United Kingdom and the European Union, women who receive valproate must use highly reliable contraception (a hormonal implant or an intrauterine device) or undergo monthly pregnancy tests, and they must sign an annual risk-acknowledgment form.[29]

Data from pregnancy registries have shown no consistent safety signals for lamotrigine or levetiracetam[30] and no clear evidence of neurodevelopmental delay associated with these agents.[31] In observational studies, maternal folate supplementation has been associated with a reduced risk of neurocognitive abnormalities among babies with in utero exposure to antiseizure medications,[32] and such supplements are routinely recommended in women who may become pregnant while receiving such medication.

#### EFFECTIVENESS OF MEDICATIONS

A single-center observational study involving 525 patients with epilepsy of various types showed that approximately half became seizure-free for at least 1 year after they began to receive a first antiseizure medication.[33] Many randomized, controlled trials of the efficacy of new antiseizure medications have assessed their use as add-on medications in patients with treatment-resistant epilepsy. In these short-term trials, these new medications reduced the frequency of seizures 2 to 4 times more than placebo[34] but often at doses that were higher than those generally used in practice.

The management of epilepsy, which is a long-term condition, is largely informed by the Standard and New Antiepileptic Drugs (SANAD) trials, which involved long-term, head-to-head, unblinded comparisons of existing standard agents with newer medications. The first SANAD trial involving patients with generalized and unclassified epilepsies compared valproate (then the standard of care) with lamotrigine or topiramate and showed the superiority of valproate over topiramate with respect to treatment failure and the superiority over lamotrigine with respect to 12-month remission.[22] For focal epilepsies, lamotrigine was superior to carbamazepine (then the standard of care), gabapentin, and topiramate with respect to treatment failure and was noninferior to carbamazepine with respect to 12-month remission.[17] More recently, the SANAD II trial involving patients with generalized and unclassified epilepsies did not show noninferiority of levetiracetam to valproate with respect to 12-month remission; valproate resulted in a higher incidence of 12-month remission (36% vs. 26%) and a similar incidence of adverse events, and it was more cost-effective.[21] For focal epilepsies, zonisamide but not levetiracetam was noninferior to lamotrigine with respect to 12-month remission; however, as compared with both levetiracetam and zonisamide, lamotrigine resulted in lower incidences of treatment failure and adverse events, and it was more cost-effective.[18]

Thus, the first-line medication for patients with generalized-onset seizures is sodium valproate, or levetiracetam for girls and women of childbearing potential. For patients with focal-onset seizures, lamotrigine is usually the first-line medication, although levetiracetam or other agents may have advantages in some patients (Table 4 and Fig. S2).

The main disadvantage of lamotrigine is its low starting dose, with increases to the full treatment dose over a period of several weeks. This gradual dose adjustment is necessary to reduce the risk of the Stevens–Johnson syndrome and toxic epidermal necrolysis (from 1.0% to approximately 0.01 to 0.10%)[35]; initial coverage with another antiseizure medication may be warranted. The main adverse effects of levetiracetam are irritability and anxiety, especially in patients with preexisting anxiety.

#### LIFESTYLE FACTORS

Clinicians should engage in joint decision making with patients and share verbal and written information. Information on driving eligibility is particularly important. In the United Kingdom and the European Union, a 6-month driving restriction is mandated for patients who have had a single seizure with a low risk of recurrence, and a 12-month restriction is mandated for patients with epilepsy, including those who have had a single seizure and who have a high risk of recurrence (e.g., those with an abnormal EEG, neurologic deficit, or both). In the United States, eligibility for a driver's license in persons who have had a single seizure or in those with epilepsy varies among states,[36] although the rules are generally less restrictive than those in Europe.

Advice from clinicians regarding other activities depends on the characteristics and frequency of the patient's seizures; these factors are balanced against individual priorities. Clinicians should inform patients of the risks associated with seizures, including drowning and SUDEP; the likelihood of seizure recurrence (Table 1); and suggested lifestyle modifications (e.g., avoiding being alone during certain activities such as caring for children or bathing, so that another

person can help if a seizure occurs, and appreciating the risks of ladders and heights).

Patients should be encouraged to adhere to the regimen of antiseizure medication and a regular sleep schedule and to limit the use of alcohol. Considerable observational data provide support for a relationship between insufficient sleep and seizure risk or abnormal EEG activity.[37] A short-term randomized trial[38] involving 84 patients with medication-resistant focal epilepsy in whom the dose of antiseizure medication was being tapered showed no significant differences in seizure frequency between the group of patients with sleep deprivation and the control group. However, these trial findings may not be applicable to patients with early epilepsy, and the promotion of sleep hygiene in patients with epilepsy remains prudent. Alcohol use is an important seizure precipitant, mainly because of the risk of seizure during alcohol withdrawal and the tendency of alcohol to disrupt sleep, interfere with adherence to antiseizure medications, or both. A meta-analysis of observational studies showed a dose–response relationship between the amount of alcohol consumed daily and the probability of development of epilepsy; for an average of 4, 6, and 8 drinks daily, the relative risks were 1.81 (95% confidence interval [CI], 1.59 to 2.07), 2.44 (95% CI, 2.00 to 2.97), and 3.27 (95% CI, 2.52 to 4.26).[39] Alcohol abstinence is probably unnecessary, but consumption should be limited to modest amounts. Illicit drugs that disrupt sleep, especially cocaine and amphetamine, should be avoided, but high-quality data on the recreational use of cannabis in persons with epilepsy are lacking.

## AREAS OF UNCERTAINTY

The clinical diagnosis of epilepsy may be incorrect in up to 20% of patients[40] unless episodes are captured on EEG with video. Many patients with a diagnosis of epilepsy are later recognized to have psychogenic seizures, and additional psychogenic seizures may later develop in persons with established epilepsy. Clinicians must repeatedly question the diagnosis in patients with medication-resistant epilepsy.

The potential long-term effects of new antiseizure medications, which are typically prescribed as lifelong treatments, warrant further study. Notoriously, for 8 years after licensing, vigabatrin was used worldwide to manage seizures until it was recognized that long-term use of this agent caused permanent visual-field defects in more than half of patients.[41] Data are lacking to inform pregnancy and offspring outcomes associated with new antiseizure medications; several worldwide pregnancy registries regularly update clinicians on the teratogenicity of these agents (Table S3).[30]

Genetic characterization has enabled both targeting of more effective treatments for some complex epilepsies (e.g., stiripentol for the Dravet syndrome[42] and a ketogenic diet for glucose transporter type 1 deficiency syndrome[43]) and screening for the HLA-B*1502 allele in Han Chinese populations to predict the carbamazepine-induced Stevens–Johnson syndrome.[44] Further understanding of the effect of genetic factors on the risk of recurrent seizures and on the efficacy and risks of various medications is needed to guide treatment decisions.

## GUIDELINES

In 2015, the American Academy of Neurology and the American Epilepsy Society provided joint guidelines on the management of unprovoked first seizure in adults.[2] The 2012 guidelines[45] of the National Institute for Health and Care Excellence in the United Kingdom are undergoing revision. The current recommendations differ from these older guidelines with respect to specific medications recommended, since the results of the SANAD II trial were published after these guidelines were issued.

## CONCLUSIONS AND RECOMMENDATIONS

In the patient described in the vignette, the first generalized tonic–clonic seizure developed after sleep loss and alcohol use. Careful questioning revealed that this was an isolated event, with no previous myoclonic jerks or absences. Evaluation should include MRI of the head, interictal EEG, and 12-lead ECG. I would discuss with the patient lifestyle factors such as the importance of regular sleep and limiting alcohol consumption, the risks associated with seizures (including drowning and SUDEP), and driving eligibility. Antiseizure medications are not routinely recommended for patients who have had a single seizure;

however, if interictal EEG showed spike-and-wave activity, indicating a high risk of recurrent seizure, I would recommend initiation of an antiseizure medication. Provided that this patient did not have depression or anxiety, I would favor levetiracetam administered with a folate supplement since the patient is of childbearing potential. I would arrange follow-up in 2 months to review the patient's response and adherence to the medication regimen and any adverse effects.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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