Emergency Management of Epilepsy and Seizures

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Abstract

Seizure- and epilepsy-related complications are a common cause of emergency medical evaluation, accounting for 5% of 911 calls and 1% of emergency department visits. Emergency physicians and neurologists must be able to recognize and treat seizure- and epilepsy-related emergencies. This review describes the emergency evaluation and management of new onset seizures, breakthrough seizures in patients with known epilepsy, status epilepticus, acute symptomatic seizures, and acute adverse effects of antiepileptic drugs.

Keywords

- new onset seizures
- breakthrough seizures
- status epilepticus
- antiepileptic drug toxicity

Seizures are a common cause of emergency medical evaluation, accounting for 5% of 911 calls and 1% of emergency department visits.[1,2] Patients with epilepsy have more frequent visits to the emergency department than the general population, with 13% of adults and 22% of children with epilepsy visiting the emergency department each year.[3,4] Emergency physicians and neurologists must be able to recognize and treat seizure- and epilepsy-related emergencies. In this review, we provide case examples and discuss the emergency evaluation and management of new onset seizures, breakthrough seizures in patients with known epilepsy, status epilepticus, acute symptomatic seizures, and acute adverse effects of antiepileptic drugs (AEDs).

Emergency Management of New Onset Seizures

Case 1

A 22-year-old woman with no significant medical history was in a meeting with coworkers when she suddenly stopped speaking. She was unable to respond to her coworkers' questions, and within seconds of the onset of unresponsiveness her eyes rolled upward, and her arms and legs stiffened. Soon afterward, she began to have rapid clonic jerking of both arms and legs. After 2 minutes, the jerking gradually slowed. She was able to say her name, but did not know where she was and was unable to recall the event. Her coworkers called 911 and she was brought to the emergency department for evaluation.

Initial Management

With any seizing patient, the immediate goal is to ensure the patient's safety while waiting for emergency services to arrive. Any objects that could injure the patient should be moved out of the way, and if possible, the patient should be moved to the floor or another flat surface to prevent falls or injuries (ideally on his or her side rather than supine to avoid aspiration). The patient's airway, breathing, and circulation should be evaluated. Fingers or other objects should not be inserted into the patient's mouth while the seizure is ongoing as this can result in aspiration or further injury.

Prehospital Emergency Response for New Onset Seizures

When emergency medical technicians arrive, the patient's airway, breathing, and circulation will be evaluated again. If the patient's airway is obstructed, suction may be needed. If the patient has low oxygen saturation, cyanosis, slowed respiratory rate, or poor respiratory effort, bag-mask ventilation should be initiated and continued until a stable airway can be obtained via intubation, either in the ambulance or upon arrival to the hospital. Even if the airway is patent, supplemental oxygen should be administered if necessary to maintain oxygen saturation above 92%.[5]

Temperature, heart rate, respiratory rate, and blood pressure should be checked upon emergency medical services (EMS) arrival and frequently while the patient is being transported to the emergency department. Glucose level should be checked using a finger-stick blood glucose monitor. For adults with a blood glucose measurement below 60 mg/dL, 100 mg of

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intravenous (IV) thiamine and 50 mL of 50% dextrose should be administered.[6] For children 2 years of age or older, 2 mL/kg of 25% dextrose should be administered.[6] For children under 2 years, 4 mL/kg of 12.5% dextrose should be administered.[6]

Most seizures will stop spontaneously by the time emergency medical personnel arrive. If the seizure is still ongoing, the patient's condition has progressed to status epilepticus, which is discussed in detail below.

Emergency Department Evaluation

If the seizure has stopped and the patient's condition has returned to baseline by the time of arrival to the emergency department, investigation into the underlying cause of the seizure can begin. If the seizure has not stopped or the patient's mental status remains impaired, treatment for status epilepticus should be initiated, as described below.

The first step in the work-up of a first time seizure is to confirm that the event was truly a seizure. Positive symptoms such as paresthesias, limb jerking, olfactory or auditory phenomena, experiential symptoms such as déjà vu, and confusion following the event are suggestive of epileptic seizures. In generalized seizures, tongue biting and urinary incontinence can also be seen.

If the patient remembers the episode or the events preceding it, elements of the history can help diagnose common seizure mimics. A prodrome of lightheadedness, nausea, and clamminess, followed by immediate return to baseline upon awakening, suggests syncope.[7] Importantly, convulsive jerking can occur during syncopal episodes,[8] and incontinence or mild tongue biting can also occur. Strokes and transient ischemic attacks are usually characterized by negative symptoms, such as weakness or vision loss.[7] Migraines typically include a headache, although some migraines are painless and include a visual aura that can be mistaken for a seizure aura.[9] Psychogenic nonepileptic seizures often include preserved awareness, asynchronous or nonrhythmic limb movements, side-to-side head shaking, ictal stuttering, grimacing, pelvic thrusting, or forced eye closure; however, this remains a diagnosis of exclusion and should be verified with video electrocephalographic (EEG) monitoring.[10]

Once common seizure mimics have been excluded, precipitating factors that can trigger provoked seizures should be ruled out as well. Alcohol withdrawal is a common cause of provoked seizures, which usually occur between 6 and 48 hours after the patient's last drink.[11] Other provoking factors include hypoglycemia, hyperglycemia, electrolyte disturbances, amphetamine, cocaine, and opiate intoxication, and benzodiazepine withdrawal, among others.[12–15] If there is suspicion for central nervous system infection, a lumbar puncture should be considered.

If the seizure was unprovoked, neuroimaging and an EEG should be obtained to look for an etiology and to decide whether to initiate treatment with an AED. A computed tomography (CT) scan should be performed in the emergency department to rule out a hemorrhage or other lesion requiring immediate treatment. A magnetic resonance imaging (MRI) scan, ideally 3 tesla, should be performed either in the emergency department or as an outpatient. MRI has the highest yield for detecting potentially epileptogenic lesions, with 23% of patients with new onset seizures having a lesion on MRI.[16] The EEG should be obtained as soon as possible after the seizure, and ideally within 12 hours of the event, as the likelihood of identifying an epileptiform abnormality decreases over time.[17]

Table 1 Predictors of recurrent seizure after a first unprovoked seizure

Predictor	Relative risk or odds of seizure recurrence	95% confidence interval
Prior brain injury[20]	2.55[a]	1.44–4.51
Abnormal EEG[21]	2.84[b]	1.67–4.82
Epileptogenic lesion on CT or MRI[22]	1.87[c]	1.24–1.83
Nocturnal seizure[23]	2.1[d]	1.0–4.3

Abbreviations: CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging.
[a]Rate ratio, multivariate Cox regression analysis.
[b]Relative risk, multivariate Cox regression analysis.
[c]Odds ratio, univariate logistic regression.
[d]Odds ratio, proportional hazards model.

Patients who are seen in the emergency department after a first unprovoked seizure will often want to know if they have epilepsy, and if they need to take an AED. A careful history should be obtained to ensure that, in retrospect, there was not a prior unrecognized seizure (such as unexplained nocturnal incontinence or bruising), as two unprovoked seizures would confirm a diagnosis of epilepsy.

While older guidelines had stated that epilepsy could only be diagnosed after two unprovoked seizures, in 2014 the International League Against Epilepsy expanded this definition, allowing epilepsy to be diagnosed after a first unprovoked seizure if the patient is thought to have a 60% or greater chance of a second unprovoked seizure within the next 10 years.[18] In practice, patients with a prior brain injury, abnormal neuroimaging or EEG findings, or nocturnal seizures typically fall into this category, as the overall risk of seizure recurrence within two years is 21 to 45%, and these predictors approximately double the risk of recurrence (►**Table 1**).[19–23]

In these cases, initiation of AED treatment in the emergency department should be considered after discussion with the patient about the benefits and risks, particularly if there might be a delay in obtaining outpatient care. If neuroimaging and an EEG cannot be obtained quickly in the emergency department, these tests should be performed in the outpatient setting, and decisions about AED treatment can be deferred to the outpatient follow-up visit.

Emergency Management of Breakthrough Seizures

Case 2

An 8-year-old boy with autism spectrum disorder, developmental delay, and intractable epilepsy developed a cough and

fever of 102°F. Despite treatment with acetaminophen and ibuprofen, his fever persisted. His left arm began to shake, followed by turning of his head to his left side, and eventually generalized shaking that persisted for several minutes. After 5 minutes of continuous shaking, his father administered rectal diazepam and called 911.

Initial Management of Breakthrough Seizures

As with the new onset seizure patient described in Case 1, the immediate goal during a seizure in a patient with known epilepsy is to ensure the patient's safety and confirm that his or her airway, breathing, and circulation are stable. Family members or others who have witnessed previous seizures will often be able to tell whether it is a typical or atypical seizure. If the seizure is typical and self-limited (resolves within 3 to 5 minutes without intervention), and the patient rapidly returns to his or her baseline mental status after the conclusion of the seizure, he or she may not require evaluation by EMS or in the emergency department.

If the seizure does not resolve quickly, however, a rescue medication should be given to abort the seizure and prevent progression to status epilepticus. Seizures that last longer than 5 minutes are unlikely to stop spontaneously.[24] If the seizure does not begin to resolve within 3 minutes, a rescue medication should be prepared. Rescue medications can also be given after the termination of a seizure in patients who have seizure clusters, to prevent additional seizures.[25]

Selection of Rescue Medications in Patients with Epilepsy

Most patients with known epilepsy should be prescribed a rescue medication, and the patient's family members or other caregivers should be counseled about the proper use of these medications. All of the available rescue medications are benzodiazepines; of these, the only Food and Drug Administration (FDA)-approved agent is rectal diazepam (Diastat).[26] Rectal administration can often be unpleasant for patients and family members, particularly once the patient is out of the early childhood years. Intranasal and buccal midazolam are fast-acting alternatives (►**Table 2**).[27–32] Oral benzodiazepines can be prescribed as rescue medications as well, but are impossible to administer while a patient is actively seizing, and thus are often more appropriate for prevention of seizure clusters.

Emergency Department Evaluation Following a Breakthrough Seizure

After an atypical or prolonged seizure, or if rescue medications are given or the patient does not rapidly return to his or her baseline mental status, evaluation in the emergency department is appropriate. A careful history aimed at the identification of possible seizure triggers should be taken (missed or delayed AED doses; recent fevers or infectious symptoms, particularly vomiting or diarrhea, as these may affect medication absorption; recent changes in medication dosing or new medications, including non-AED medications; and sleep deprivation or other physiologic or emotional stressors).

Basic laboratory studies, including a basic metabolic panel, complete blood count, and liver function tests, are often ordered but are rarely abnormal. Similarly, CT scans rarely show acute abnormalities.[33] We recommend ordering a CT scan for patients who experienced an atypical seizure or head trauma during the seizure, have an abnormal neurological exam after the seizure, are immunocompromised or taking anticoagulant or antiplatelet medications, or have a known intracranial lesion.

AED levels should be ordered for patients who present with a breakthrough seizure. Unfortunately, most drug levels take several hours to days to report and thus this information often does not change management while the patient is still in the emergency department. Lamotrigine, carbamazepine, oxcarbazepine, phenytoin, and valproic acid have relatively standard therapeutic ranges, and dose adjustments can be made if a low level returns before the patient leaves the emergency department. For all other AEDs, levels are primarily useful for assessing medication compliance or changes in absorption and can be very useful to the treating physician even if not immediately available.

Table 2 Commonly prescribed rescue medications for seizure cessation

Medication	Route	Adult Dosing	Pediatric Dosing
Diazepam[27,28]	Rectal	0.2 mg/kg (up to 20 mg)	2–5 y: 0.5 mg/kg 6–11 y: 0.3 mg/kg 12+ y: 0.2 mg/kg (up to 20 mg)
Midazolam[29–31]	Intranasal	0.2 mg/kg	1–5 mo: 0.2 mg/kg ≥6 mo: 0.2–0.3 mg/kg (up to 10 mg)
Midazolam[29,30,32]	Buccal	0.5 mg/kg	Weight-based dosing ≥3 mo: 0.2–0.5 mg/kg (up to 10 mg) Age-based dosing 6–11 mo: 2.5 mg 1–4 y: 5 mg 5–9 y: 7.5 mg ≥10 y: 10 mg

Status Epilepticus

Case 3

A 45-year-old woman with focal epilepsy secondary to a right frontal meningioma had a tonic–clonic seizure at home. Three minutes into the seizure, she continued to convulse and her husband called 911. When the ambulance arrived 10 minutes into the seizure, the emergency medical technicians placed an IV and treated her with 4 mg of IV lorazepam. The seizure continued, prompting a second dose of lorazepam. Upon arrival to the emergency department, the seizure had stopped, but the patient could not speak or follow commands, and remained plegic on the left side. A 20 mg/kg dose of IV fosphenytoin was ordered. As the medication was being administered, she began to convulse again. She was intubated, treated with an IV midazolam drip, and transferred to the intensive care unit.

Prehospital Management of Status Epilepticus

While various definitions have been proposed, the most commonly accepted definition of status epilepticus is seizure activity lasting 5 minutes or longer, or recurrent seizure activity without return to baseline in between seizures.[29] The first step in the management of status epilepticus is the same as in new onset or breakthrough seizures: evaluation of the patient's airway, breathing, and circulation, which should be monitored continuously en route to the emergency department. Attempts should be made to resolve any airway obstruction, and bag-mask ventilation should be provided if respiration is compromised. Temperature, heart rate, respiratory rate, blood pressure, and blood glucose level should be checked.

A benzodiazepine should be administered as quickly as possible. If IV access can be rapidly obtained, IV lorazepam should be administered (4 mg for adult patients and 0.1 mg/kg for pediatric patients).[29,34] If IV access cannot be obtained, intramuscular midazolam should be administered (10 mg for adults and children weighing more than 40 kg or 5 mg for children who weigh more than 13 kg; no dose data are available for children weighing less than 13 kg).[35,36] If a patient has a known allergy to lorazepam or midazolam, or these medications are not available, 5 to 10 mg of IV diazepam can also be given, although this has been shown to be less effective than lorazepam.[37]

In-Hospital Management of Status Epilepticus

Airway, breathing, and circulation should be assessed again upon arrival to the emergency department, particularly as the patient's respiratory status may be depressed following benzodiazepine administration. Vital signs, blood glucose level, and electrocardiogram (EKG) should be checked. Laboratory tests (basic metabolic panel, complete blood count, toxicology screen, and AED levels if the patient has known epilepsy) should be obtained.[6]

Within the first 5 minutes, a benzodiazepine (IV lorazepam, intramuscular diazepam, or IV diazepam) should be administered if it was not given prior to arrival. IV lorazepam and diazepam can be given a second time if the seizure is ongoing.[6]

Within the first 20 minutes, an IV AED should be given. The American Epilepsy Society recommends fosphenytoin (20 mg/kg, up to 1,500 mg), valproic acid (40 mg/kg, up to 3,000 mg), levetiracetam (60 mg/kg, up to 4,500 mg), or phenobarbital (15 mg/kg).[6] Lacosamide (5 mg/kg, or 400 mg for an adult patient) has been shown to be effective in treating status epilepticus in retrospective studies; a prospective study comparing lacosamide to fosphenytoin for the treatment of nonconvulsive status epilepticus is ongoing.[38,39]

If the patient continues to have seizures after treatment with a benzodiazepine and an IV AED, he or she now has refractory status epilepticus, and third-line treatment should be initiated within the first hour.[29] If the patient is still breathing well, a second IV AED can be given. If the second AED fails or if there are any signs of respiratory compromise, the patient should be intubated and treated with a continuous infusion of midazolam, propofol, or pentobarbital (►**Table 3**).[6,29]

Symptomatic Seizures and Seizure Prophylaxis in Acute Neurologic Disease

Case 4

A 78-year-old man with atrial fibrillation on warfarin tripped on the sidewalk, fell, and hit his head. He did not lose consciousness, but complained of a headache and tingling in his right arm. He was brought to the emergency department where a CT scan showed a 1-cm left-hemispheric subdural hematoma. Anticoagulation was held, and prophylactic treatment with levetiracetam 750 mg twice a day was initiated. Repeat scans over the next several days showed a stable bleed. He did not have any clinical or electrographic seizures. Levetiracetam was discontinued after 7 days, and he remained seizure-free.

Seizure Treatment and Prophylaxis in Patients with Intracranial Hemorrhages

Intracranial hemorrhages can present with or precipitate acute symptomatic seizures. Patients with acute symptomatic seizures secondary to intracranial hemorrhage should

Table 3 Dosing of continuous infusions for treatment of refractory status epilepticus[29]

Medication	Initial dose	Starting infusion dose	Bolus dose	Maximum infusion dose
Midazolam	0.2 mg/kg at an infusion rate of 2 mg/min	0.05 mg/kg/h	0.1–0.2 mg/kg	2 mg/kg/h
Propofol	1–2 mg/kg at an infusion rate of 20 mcg/kg/min	20 mcg/kg/min	1 mg/kg	200 mcg/kg/min
Pentobarbital	5–15 mg/kg at an infusion rate of $\leq$50 mg/min	0.5 mg/kg/h	5 mg/kg	5 mg/kg/h

be treated with an AED, and treatment should continue until the underlying insult has resolved.[40] For patients with intracranial bleeding who have not had seizures, AED prophylaxis is often started reflexively in the emergency department by emergency physicians or consulting neurologists or neurosurgeons, but the evidence for doing so is limited and this remains controversial.

Subdural Hematoma

The incidence of early posttraumatic seizures (within the first 7 days) after an acute traumatic subdural hematoma is 15 to 36%.[41] A 7-day course of AED prophylaxis (most commonly levetiracetam 750 mg twice a day in patients with normal renal function) is often given to patients with acute subdural hematomas, though the evidence for doing so is indirect. In a randomized prospective trial comparing phenytoin to placebo for prevention of seizures within the first 7 days after traumatic brain injury, significantly fewer patients in the treatment group had seizures (3.6% compared with 14.2%).[42] Thirty-five percent of patients in the treatment group and 42% in the placebo group had subdural hematomas, though the incidence of seizures within the subdural hematoma subgroup was not reported.[42] A recent retrospective study showed no difference between phenytoin and levetiracetam for seizure prevention after acute subdural hematoma, suggesting that levetiracetam may be a better choice as it is better tolerated and does not require drug level monitoring.[43]

Subarachnoid Hemorrhage

Acute symptomatic seizures are also common after subarachnoid hemorrhage, with estimates of the incidence ranging from 6 to 26%.[44] As with subdural hematomas, an AED should be initiated if the patient has a clinical or electrographic seizure. Some authors have suggested that in cases of aneurysmal subarachnoid hemorrhage, AED prophylaxis should be initiated immediately and continued until the aneurysm is secured, due to the theoretical risk of repeated rupture if the patient were to have a convulsive seizure.[44] Although prophylactic AEDs are often initiated in patients with subarachnoid hemorrhage, typically for 7 days after the initial bleed, a recent prospective study showed that this does not reduce the risk of seizures.[45]

Many patients with aneurysmal subarachnoid hemorrhage who undergo craniotomy for aneurysm clipping will be treated with a short course of AED prophylaxis at the recommendation of the neurosurgeon. Of note, however, the evidence for the use of AED prophylaxis to prevent postcraniotomy seizures is equivocal, with one study[46] showing fewer seizures in the treated group and another showing no difference.[47]

Intraparenchymal Hemorrhage

Acute symptomatic seizure rates following intraparenchymal hemorrhage range from 7 to 17%.[44] Again, symptomatic seizures should be treated until the acute insult has resolved, but prophylactic treatment has not been shown to be effective in preventing early seizures.[48]

Summary of Seizure Prophylaxis for Patients with Intracranial Hemorrhage

Overall, despite the high incidence of intracranial hemorrhage and the frequent occurrence of acute symptomatic seizures in this population, the evidence to support prophylactic AED treatment is limited. Based on the available data, we recommend prophylaxis for patients with traumatic subdural hematoma. For patients with subarachnoid hemorrhage or intraparenchymal hemorrhage, seizure prophylaxis need not be started automatically in all patients, but should be considered in patients with unsecured ruptured aneurysms, patients undergoing craniotomy, and other patients in whom early seizures are considered likely (e.g., patients with epileptiform abnormalities on continuous EEG).

Seizure Treatment in Patients with Brain Tumors

Hemorrhages are not the only intracranial lesions that can present with or precipitate seizures requiring emergent evaluation. Seizures are common in patients with brain tumors, and are often the first symptom, with approximately 20% of patients with brain metastases and 40% of patients with primary brain tumors initially presenting with seizures.[49] Patients with previously undiagnosed or known brain tumors who present for emergency evaluation following a first seizure meet the criteria for a diagnosis of epilepsy, as they have a greater than 60% chance of recurrent unprovoked seizures. Thus, AED treatment is indicated.

Evidence favoring the use of one AED over another is limited. Enzyme-inducing AEDs are often avoided due to their potential interactions with chemotherapy.[50] Levetiracetam monotherapy (starting dose of 500–750 mg twice a day) is often used as first-line treatment due to its lack of drug interactions and absence of side effects in most patients.[50] In patients with psychiatric comorbidities, valproic acid (titrated to a serum level of 70–100) and lacosamide (starting dose of 100 mg twice a day) are reasonable alternatives.[50,51] Monotherapy using phenytoin (despite its complicated drug interactions) and pregabalin has been described as well.[52,53]

Seizure Prophylaxis in Patients with Brain Tumors

Patients are often diagnosed with brain tumors in the emergency department after presenting with headaches, focal weakness, or other nonseizure neurologic abnormalities. An American Academy of Neurology guideline published in 2000 recommended against prophylactic AED treatment in brain tumor patients without seizures, as the benefit of first-time seizure prevention is outweighed by the risk of side effects.[54]

Seizure Treatment in Patients with Ischemic Strokes

Seizures can also occur as the presenting symptom of an acute ischemic stroke.[55] In the emergency room setting, the most important question for these patients is whether or not to administer IV tissue-type plasminogen activator (tPA). The American Heart Association/American Stroke Association guidelines consider seizure at onset to be a relative contraindication to tPA administration, with the rationale that unilateral focal deficits may represent Todd's paralysis rather than focal ischemia.[56] However, studies have shown that tPA

administration is safe in patients with seizures at the onset of stroke-like symptoms, and 91% of stroke neurologists report that they would recommend tPA for a patient with seizure at onset if no other contraindications were present.[57,58]

Most authors draw a distinction between acute symptomatic (early) and remote symptomatic (late) poststroke seizures, with definitions of the acute symptomatic period ranging from 7 to 30 days after the stroke.[59–61] Estimates of the incidence of acute symptomatic seizures vary widely, but most studies suggest that the rate is approximately 5%.[59,60] Some patients with acute symptomatic seizures after stroke will later develop unprovoked seizures, with a recent study reporting the incidence as 16% at 1 year, 19% at 2 years, 25% at 4 years, and 28% at 8 years.[62] Because these rates are relatively low, long-term AED treatment for patients with seizures at stroke onset or within the acute period is not routinely recommended. In practice, short courses (1–4 weeks) of AEDs are often prescribed, with the thought that this may prevent additional acute symptomatic seizures.

The risk of remote symptomatic seizures increases with the amount of time after the stroke, with 3.1% of patients having a seizure within the first year and 5.5% of patients having a seizure within 3 years.[60] Importantly, patients with remote symptomatic seizures are more likely to develop recurrent unprovoked seizures, with as many as 90% of patients going on to develop poststroke epilepsy.[63] Thus, patients who present for emergency evaluation with a new onset seizure and a remote history of stroke in the same brain territory are typically treated with an AED. Evidence favoring the use of one AED over another is limited. Levetiracetam is often chosen because of its efficacy and favorable side-effect profile.[64,65]

Seizure Prophylaxis in Patients with Ischemic Strokes

Prophylactic treatment with AEDs in poststroke patients who have not had a seizure is not currently recommended, though a prospective randomized trial has been proposed.[66,67]

Acute Presentations of Antiepileptic Drug Toxicity

Case 5

A 35-year-old woman presented to the emergency department with severe left-sided abdominal pain. She reported that for the prior 2 days she needed to urinate constantly, but urination was painful and she noticed blood in her urine. A CT scan of the abdomen and pelvis showed a stone in the left ureter. She was admitted to the hospital and treated with IV fluids and pain medications. Upon review of her past medical history and medication list, the admitting doctor realized that she had longstanding right temporal lobe epilepsy and had been taking topiramate for several years.

Emergency Evaluation and Management of Antiepileptic Drug Toxicity

While most AEDs, particularly the older ones, have adverse effects, many of these effects are chronic and are typically managed in the outpatient setting. However, some AED side effects develop acutely and necessitate emergent evaluation. It is essential that a careful medication history be taken in all patients with epilepsy to identify the role the patient's AEDs may play in their acute medical conditions. Common specific examples and their management are described below.

Acute Peak Dose Central Nervous System Effects of Antiepileptic Drugs

Dizziness, diplopia, ataxia, vision changes, and lethargy are common complaints among patients presenting to the emergency department. These complaints typically (and reasonably) lead to evaluation for ischemic stroke and other acute neurologic diseases. Once these diagnoses have been ruled out, however, drug toxicity should be considered as a potential explanation in any patient taking AEDs. Reversible adverse central nervous system effects have been reported with nearly all of the available AEDs, and typically occur between 20 minutes and 1 hour after dose administration, when the serum level peaks.[68]

Peak dose effects are most commonly seen after starting a new AED or after a dose increase, but can also occur with a compliant patient on a steady dose if changes in other medications change the AED's metabolism (most often, removal of an enzyme-inducing agent will result in increasing AED levels over several weeks). When patients present with acute central nervous system complaints attributable to AEDs, the offending drug should be held until the symptoms have resolved, and then started at a lower dose. If symptoms recur at a lower dose, switching to an alternative AED should be considered.

Kidney Stones Associated with Topiramate and Zonisamide Use

Early studies of topiramate use showed a two- to four-fold increase in the risk of kidney stones compared with the general population.[69] While a more recent study failed to confirm this increased risk,[70] topiramate is associated with increased urinary pH, decreased urinary citrate excretion, and increased sodium, calcium, and oxalate excretion, which can increase the risk of stone formation.[69] Zonisamide is also associated with an increased risk of kidney stones.[71]

Alternative anticonvulsant therapy should be considered in patients taking topiramate or zonisamide who develop stones. In most cases, the drug should be permanently discontinued, but in patients with refractory epilepsy who have responded uniquely well to the offending drug, continuation of treatment can be considered.[72]

Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis and Antiepileptic Drug Use

Stevens–Johnson syndrome and toxic epidermal necrolysis are life-threatening dermatologic illnesses characterized by rashes and bullous lesions involving the skin and oral, nasal, genitourinary, gastrointestinal, and respiratory tract mucosa.[73] Although both syndromes are classically associated with lamotrigine, cases involving phenytoin, carbamazepine, phenobarbital, and less frequently valproic acid have also been described.[74,75] A dermatologist should be consulted and the AED should be stopped immediately in patients with Stevens–Johnson syndrome or toxic epidermal necrolysis, as early drug cessation is associated with decreased mortality.[73]

Due to the high morbidity and mortality associated with these diseases, lamotrigine in particular is often stopped when a patient develops any rash. While this cautious approach is reasonable in patients whose seizures can be controlled with an alternative agent, patients with refractory epilepsy in whom the current AED has been effective should be evaluated by dermatology to determine whether the rash is truly consistent with Stevens–Johnson syndrome or toxic epidermal necrolysis prior to permanently stopping the drug.

Hyponatremia Associated with Carbamazepine and Oxcarbazepine Use

Symptoms of hyponatremia are often nonspecific and include confusion, fatigue, headaches, and generalized weakness. Physicians should have a low threshold to order a basic metabolic panel and AED levels in epilepsy patients who present with these symptoms, particularly if they are taking carbamazepine or oxcarbazepine. In a recent study, 28% of patients taking carbamazepine and 46% of patients taking oxcarbazepine were hyponatremic (sodium level $\leq$ 134 mEq/L), while 7% of those taking carbamazepine and 22% of those taking oxcarbazepine were severely hyponatremic (sodium level $\leq$ 128 mEq/L).[76] Thirty-five percent of the patients with mild hyponatremia and 72% of the patients with severe hyponatremia were symptomatic.[76] Sodium levels were significantly associated with AED levels for both medications.[76]

In patients whose seizures are well controlled and who develop hyponatremia while on oxcarbazepine or carbamazepine, it is reasonable to try reducing the dose, as seizures may remain controlled on a lower dose that does not lower the sodium level below the normal range. However, if the seizures are poorly controlled and lowering the dose is not reasonable, cross-titration to a different AED is indicated.

Hyperammonemia Associated with Valproic Acid

As with hyponatremia, symptoms of hyperammonemia are nonspecific, and may include vomiting, decreased appetite, ataxia, confusion, or increased seizure frequency. If untreated, these symptoms can progress to cerebral edema, coma, and death. All patients treated with valproic acid who present with one or more of these symptoms should have an ammonia level checked. Discontinuation of valproic acid is the most effective treatment for hyperammonemia.[77] Adjunctive therapy with levocarnitine and lactulose has been reported.[77,78] Of note, many patients treated with valproic acid develop asymptomatic hyperammonemia; routine screening for hyperammonemia in asymptomatic patients and discontinuation of valproic acid in patients with asymptomatic hyperammonemia is not recommended.[79,80]

Conclusion

Patients with seizures and epilepsy frequently require emergency medical evaluation, with causes ranging from status epilepticus to medical complications resulting from AED therapy. Emergency physicians and neurologists should feel comfortable managing the most common complaints, including new onset seizures, breakthrough seizures, status epilepticus, acute symptomatic seizures, and AED toxicity.

Conflict of Interest
None declared.

References

1 Johnston C, King WD. Pediatric prehospital care in a southern regional emergency medical service system. South Med J 1988;81 (12):1473–1476
2 Pallin DJ, Goldstein JN, Moussally JS, Pelletier AJ, Green AR, Camargo CA Jr. Seizure visits in US emergency departments: epidemiology and potential disparities in care. Int J Emerg Med 2008;1(02):97–105
3 Noble AJ, Goldstein LH, Seed P, Glucksman E, Ridsdale L. Characteristics of people with epilepsy who attend emergency departments: prospective study of metropolitan hospital attendees. Epilepsia 2012;53(10):1820–1828
4 Jacoby A, Buck D, Baker G, McNamee P, Graham-Jones S, Chadwick D. Uptake and costs of care for epilepsy: findings from a U.K. regional study. Epilepsia 1998;39(07):776–786
5 Michael GE, O'Connor RE. The diagnosis and management of seizures and status epilepticus in the prehospital setting. Emerg Med Clin North Am 2011;29(01):29–39
6 Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. Epilepsy Curr 2016;16(01):48–61
7 Webb J, Long B, Koyfman A. An emergency-medicine focused review of seizure mimics. J Emerg Med 2017;52(05):645–653
8 Izumi M, Okabe T, Komura M, Hayashi Y. Convulsive syncope on electroencephalogram. J Gen Fam Med 2018;19(03): 109–110
9 Hartl E, Gonzalez-Victores JA, Rémi J, Schankin CJ, Noachtar S. Visual auras in epilepsy and migraine – an analysis of clinical characteristics. Headache 2017;57(06):908–916
10 Chen DK, Sharma E, LaFrance WC Jr. Psychogenic non-epileptic seizures. Curr Neurol Neurosci Rep 2017;17(09):71
11 Hillbom M, Pieninkeroinen I, Leone M. Seizures in alcohol-dependent patients: epidemiology, pathophysiology and management. CNS Drugs 2003;17(14):1013–1030
12 Imad H, Zelano J, Kumlien E. Hypoglycemia and risk of seizures: a retrospective cross-sectional study. Seizure 2015;25:147–149
13 Wang X, Yu H, Cai Z, Wang Z, Ma B, Zhang Y. Nonketotic hyperglycemia-related epileptic seizures. Epilepsy Behav Case Rep 2013;1:77–78
14 Halawa I, Andersson T, Tomson T. Hyponatremia and risk of seizures: a retrospective cross-sectional study. Epilepsia 2011; 52(02):410–413
15 Leach JP, Mohanraj R, Borland W. Alcohol and drugs in epilepsy: pathophysiology, presentation, possibilities, and prevention. Epilepsia 2012;53(Suppl 4):48–57
16 Hakami T, McIntosh A, Todaro M, et al. MRI-identified pathology in adults with new-onset seizures. Neurology 2013;81(10): 920–927
17 Sofat P, Teter B, Kavak KS, Gupta R, Li P. Time interval providing highest yield for initial EEG in patients with new onset seizures. Epilepsy Res 2016;127:229–232
18 Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(04): 475–482

19 Krumholz A, Shinnar S, French J, Gronseth G, Wiebe S. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2015;85(17):1526–1527
20 Hauser WA, Rich SS, Annegers JF, Anderson VE. Seizure recurrence after a 1st unprovoked seizure: an extended follow-up. Neurology 1990;40(08):1163–1170
21 Chen T, Si Y, Chen D, et al. The value of 24-hour video-EEG in evaluating recurrence risk following a first unprovoked seizure: a prospective study. Seizure 2016;40:46–51
22 Kho LK, Lawn ND, Dunne JW, Linto J. First seizure presentation: do multiple seizures within 24 hours predict recurrence? Neurology 2006;67(06):1047–1049
23 Bora I, Seçkin B, Zarifoglu M, Turan F, Sadikoglu S, Ogul E. Risk of recurrence after first unprovoked tonic-clonic seizure in adults. J Neurol 1995;242(03):157–163
24 Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol 2001;49(05): 659–664
25 Poukas VS, Pollard JR, Anderson CT. Rescue therapies for seizures. Curr Neurol Neurosci Rep 2011;11(04):418–422
26 Gaínza-Lein M, Benjamin R, Stredny C, McGurl M, Kapur K, Loddenkemper T. Rescue medications in epilepsy patients: a family perspective. Seizure 2017;52:188–194
27 Dreifuss FE, Rosman NP, Cloyd JC, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. N Engl J Med 1998;338(26):1869–1875
28 Diazepam: Drug information. Available at: Uptodate.com. Accessed July 17, 2018
29 Brophy GM, Bell R, Claassen J, et al; Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17(01):3–23
30 Midazolam: Drug information. Available at: Uptodate.com. Accessed July 17, 2018
31 Scheepers M, Scheepers B, Clarke M, Comish S, Ibitoye M. Is intranasal midazolam an effective rescue medication in adolescents and adults with severe epilepsy? Seizure 2000;9(06): 417–422
32 McIntyre J, Robertson S, Norris E, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet 2005;366(9481):205–210
33 Allen L, Jones CT. Emergency department use of computed tomography in children with epilepsy and breakthrough seizure activity. J Child Neurol 2007;22(09):1099–1101
34 Abend NS, Loddenkemper T. Pediatric status epilepticus management. Curr Opin Pediatr 2014;26(06):668–674
35 Silbergleit R, Durkalski V, Lowenstein D, et al; NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366(07):591–600
36 Welch RD, Nicholas K, Durkalski-Mauldin VL, et al; Neurological Emergencies Treatment Trials (NETT) Network Investigators. Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. Epilepsia 2015;56(02):254–262
37 Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345(09):631–637
38 Santamarina E, González-Cuevas M, Toledo M, et al. Intravenous lacosamide (LCM) in status epilepticus (SE): Weight-adjusted dose and efficacy. Epilepsy Behav 2018;84:93–98
39 Husain AM. Treatment of recurrent electrographic non-convulsive seizures (TRENdS) study. Epilepsia 2013;54(Suppl 6): 84–88
40 Beleza P. Acute symptomatic seizures: a clinically oriented review. Neurologist 2012;18(03):109–119
41 Won S-Y, Konczalla J, Dubinski D, et al. A systematic review of epileptic seizures in adults with subdural haematomas. Seizure 2017;45:28–35
42 Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990;323(08): 497–502
43 Radic JAE, Chou SH-Y, Du R, Lee JW. Levetiracetam versus phenytoin: a comparison of efficacy of seizure prophylaxis and adverse event risk following acute or subacute subdural hematoma diagnosis. Neurocrit Care 2014;21(02):228–237
44 Gilmore E, Choi HA, Hirsch LJ, Claassen J. Seizures and CNS hemorrhage: spontaneous intracerebral and aneurysmal subarachnoid hemorrhage. Neurologist 2010;16(03):165–175
45 Panczykowski D, Pease M, Zhao Y, et al. Prophylactic antiepileptics and seizure incidence following subarachnoid hemorrhage: a propensity score-matched analysis. Stroke 2016;47(07):1754–1760
46 North JB, Penhall RK, Hanieh A, Frewin DB, Taylor WB. Phenytoin and postoperative epilepsy. A double-blind study. J Neurosurg 1983;58(05):672–677
47 Foy PM, Chadwick DW, Rajgopalan N, Johnson AL, Shaw MDM. Do prophylactic anticonvulsant drugs alter the pattern of seizures after craniotomy? J Neurol Neurosurg Psychiatry 1992;55(09): 753–757
48 Gilad R, Boaz M, Dabby R, Sadeh M, Lampl Y. Are post intracerebral hemorrhage seizures prevented by anti-epileptic treatment? Epilepsy Res 2011;95(03):227–231
49 Lynam LM, Lyons MK, Drazkowski JF, et al. Frequency of seizures in patients with newly diagnosed brain tumors: a retrospective review. Clin Neurol Neurosurg 2007;109(07):634–638
50 Englot DJ, Chang EF, Vecht CJ. Epilepsy and brain tumors. Handb Clin Neurol 2016;134:267–285
51 Villanueva V, Saiz-Diaz R, Toledo M, et al. NEOPLASM study: real-life use of lacosamide in patients with brain tumor-related epilepsy. Epilepsy Behav 2016;65:25–32
52 Iuchi T, Kuwabara K, Matsumoto M, Kawasaki K, Hasegawa Y, Sakaida T. Levetiracetam versus phenytoin for seizure prophylaxis during and early after craniotomy for brain tumours: a phase II prospective, randomised study. J Neurol Neurosurg Psychiatry 2015;86(10):1158–1162
53 Rossetti AO, Jeckelmann S, Novy J, Roth P, Weller M, Stupp R. Levetiracetam and pregabalin for antiepileptic monotherapy in patients with primary brain tumors. A phase II randomized study. Neuro-oncol 2014;16(04):584–588
54 Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;54(10):1886–1893
55 Abend NS, Beslow LA, Smith SE, et al. Seizures as a presenting symptom of acute arterial ischemic stroke in childhood. J Pediatr 2011;159(03):479–483
56 Jauch EC, Saver JL, Adams HP Jr, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44(03):870–947
57 Chernyshev OY, Martin-Schild S, Albright KC, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. Neurology 2010;74(17):1340–1345
58 De Los Rios F, Kleindorfer DO, Guzik A, et al; SPOTRIAS Investigators. Intravenous fibrinolysis eligibility: a survey of stroke clinicians' practice patterns and review of the literature. J Stroke Cerebrovasc Dis 2014;23(08):2130–2138
59 Beghi E, D'Alessandro R, Beretta S, et al; Epistroke Group. Incidence and predictors of acute symptomatic seizures after stroke. Neurology 2011;77(20):1785–1793

60 Lamy C, Domigo V, Semah F, et al; Patent Foramen Ovale and Atrial Septal Aneurysm Study Group. Early and late seizures after cryptogenic ischemic stroke in young adults. Neurology 2003; 60(03):400–404
61 Stefanidou M, Das RR, Beiser AS, et al. Incidence of seizures following initial ischemic stroke in a community-based cohort: The Framingham Heart Study. Seizure 2017;47: 105–110
62 Leung T, Leung H, Soo YO, Mok VC, Wong KS. The prognosis of acute symptomatic seizures after ischaemic stroke. J Neurol Neurosurg Psychiatry 2017;88(01):86–94
63 Sung C-Y, Chu N-S. Epileptic seizures in thrombotic stroke. J Neurol 1990;237(03):166–170
64 Belcastro V, Costa C, Galletti F, et al. Levetiracetam in newly diagnosed late-onset post-stroke seizures: a prospective observational study. Epilepsy Res 2008;82(2-3):223–226
65 Kutlu G, Gomceli YB, Unal Y, Inan LE. Levetiracetam monotherapy for late poststroke seizures in the elderly. Epilepsy Behav 2008;13 (03):542–544
66 Silverman IE, Restrepo L, Mathews GC. Poststroke seizures. Arch Neurol 2002;59(02):195–201
67 Arboix A, García-Eroles L, Massons JB, Oliveres M, Comes E. Predictive factors of early seizures after acute cerebrovascular disease. Stroke 1997;28(08):1590–1594
68 Toledano R, Gil-Nagel A. Adverse effects of antiepileptic drugs. Semin Neurol 2008;28(03):317–327
69 Lamb EJ, Stevens PE, Nashef L. Topiramate increases biochemical risk of nephrolithiasis. Ann Clin Biochem 2004;41(Pt 2): 166–169
70 Shen AL, Lin HL, Tseng YF, Lin HC, Hsu CY, Chou CY. Topiramate may not increase risk of urolithiasis: a nationwide population-based cohort study. Seizure 2015;29:86–89
71 Kubota M, Nishi-Nagase M, Sakakihara Y, et al. Zonisamide - induced urinary lithiasis in patients with intractable epilepsy. Brain Dev 2000;22(04):230–233
72 Richards KC, Smith MC, Verma A. Continued use of zonisamide following development of renal calculi. Neurology 2005;64(04): 763–764
73 Garcia-Doval I, LeCleach L, Bocquet H, Otero X-L, Roujeau J-C. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol 2000;136(03):323–327
74 Frey N, Bodmer M, Bircher A, et al. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptic drugs. Epilepsia 2017;58(12):2178–2185
75 Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. Neurology 2005;64(07):1134–1138
76 Berghuis B, van der Palen J, de Haan G-J, Lindhout D, Koeleman BPC, Sander JW; EpiPGX Consortium. Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. Epilepsia 2017;58(07):1227–1233
77 Baddour E, Tewksbury A, Stauner N. Valproic acid-induced hyperammonemia: Incidence, clinical significance, and treatment management. Ment Health Clin 2018;8(02):73–77
78 Mock CM, Schwetschenau KH. Levocarnitine for valproic-acid-induced hyperammonemic encephalopathy. Am J Health Syst Pharm 2012;69(01):35–39
79 Murphy JV, Marquardt K. Asymptomatic hyperammonemia in patients receiving valproic acid. Arch Neurol 1982;39(09):591–592
80 Chicharro AV, de Marinis AJ, Kanner AM. The measurement of ammonia blood levels in patients taking valproic acid: looking for problems where they do not exist? Epilepsy Behav 2007;11(03): 361–366