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COMMENTARY

Management of breakthrough seizures in the emergency department: continuity of patient care

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ABSTRACT

Background: Epilepsy is a chronic disorder requiring long-term management. Communication between emergency physicians, neurologists, and primary care physicians (PCPs) is especially critical for the continuity of care for patients who present in an emergency department (ED) with a breakthrough seizure. Therefore, maximizing communication between the emergency physician and the PCP is of the utmost importance. The emergency physician, who is on the front line, must gather the information necessary to identify the underlying cause of the seizure and decide whether the pharmaceutical management must be changed.

Scope: This paper provides a clinical commentary on issues to consider when managing breakthrough seizures in the ED, to inform and facilitate communication between emergency physicians, consulting neurologists, and PCPs.

Conclusions: Clinical management decisions, especially when considering adjustment in an antiepileptic drug (AED) regimen, are often best made in coordination with a consulting neurologist. Increasing emergency physicians' comfort level regarding the use of newer-generation AEDs can improve the dialogue between the emergency physician and neurologist and the dialogue with the patient. Understanding the risks and benefits of the newer AEDs will assist the emergency physician in clinical decision making and, it is hoped, improve clinical outcomes. To preserve continuity of patient care, a patient's treating physician should be notified of all the particulars of the ED visit, and an appointment should be scheduled at the time of discharge for follow-up evaluation.

Introduction

The current prevalence of epilepsy in the United States is reported to be 1% of the general population, or close to three million cases[1,2]. Unfortunately, approximately 20–30% of patients treated for epilepsy continue to experience seizures[3,4]. When breakthrough seizures occur in patients who are otherwise controlled, some seek medical attention first from an emergency

physician rather than their treating neurologist or primary care physician (PCP).

Preserving continuity of care for patients experiencing a breakthrough seizure requires coordination with the physician who will assume care after the patient is discharged from the emergency department (ED). More often than not, communication with the outpatient physician at the time of discharge is incomplete or absent. To preserve the transition of care, emergency physicians should provide patients with a summary of physical and laboratory findings, any changes in medications, and arrangements for a follow-up appointment[5]. A recent study found that ED patients who have their outpatient follow-up appointments made at the time of discharge are more likely to comply with outpatient follow-up care[6].

Continuity of care can also be broadly interpreted in terms of patient outcomes, which may be improved by specialty consultations when indicated. While the most common cause of a breakthrough seizure is a sub-therapeutic level of antiseizure medication, a determination of cause and course of action is not always straightforward. This paper provides clinically relevant information on ED management of breakthrough seizures that can promote and facilitate communication with consulting neurologists when it is appropriate and access is available.

Since limitations of older antiepileptic drugs (AEDs) (such as adverse effects [AEs] and drug interactions) are factors in non-adherence that can play a causative role in breakthrough seizures[7–9], this article also provides a comparative overview of older and newer antiseizure-treatment options, comparing indications, pharmacokinetic features, notable side effects, and precautions or warnings (please see the accompanying tables, listing the indications (Table 1), pharmacokinetic features (Table 2), notable side effects (Table 3), and precautions or warnings (Table 4) of the newer oral AEDs).

Key concepts covered in this paper are the facts that breakthrough seizures are not uncommon in the ED and represent clinically significant events; poor adherence with an AED regimen is the most common cause of breakthrough seizures; most newer-generation AEDs have clinical profiles that promote adherence; consultation with a neurologist can ensure an AED choice is appropriate for a patient; and patient

Table 1. *Antiepileptic drug indications*[4,9,15,22–24,38,41–52]

AED	Partial Onset Seizures			Generalized Seizures				Mono-therapy
	Simple Partial	Complex Partial	Secondarily Generalized	Absence	Myoclonic	Generalized Tonic-clonic	Lennox-Gastaut	
Carbamazepine	√*	√*	√*	X*	X*	√*	X*	√*
Felbamate†	√*	√*	√*	X*	X*	X*	√*	√*
Gabapentin	√*	√*	√*	X[23,38,‡]	X*	√‡/X[23,§]	X*	X*√/[18,23,38,‡]
Lamotrigine	√*	√*	√*	√[4,22,23,38,‡]	X[15,‡,‖]	√[4,22,38,‡]	√*	√*
Levetiracetam	√*	√*	√*	X[38,‡]/√[15,§]	√*	√[4,23,§]	√[4,‡]	X*√/[18,42,‡]
Oxcarbazepine	√*	√*	√*	X[23,§]	X[15,23,‡]	√[4,38,‡]	X[23,§]	√*
Phenytoin	√*	√*	√*	X*	X*	√*	X*√[23,§]	√*
Pregabalin	√*	√*	√*	X*	X*	X*	X*	X*
Tiagabine	√*	√*	√*	X[15,23,38,‡]	X[23,§]	X*	X[23,§]	X*√[18,23,‡]
Topiramate	√*	√*	√*	X[38,‡]/√[23,§]	√[23,§]	√*	√*	√*
Valproic Acid	√*	√*	√*	√*	√[9,23,‡]	√[4,23,‡]	√[4,23,§]	√*
Zonisamide	√*	√*	√*	X[38,‡]√[15,22,23,§]	√[15,22,23,§]	√[15,22,23,§]	√[15,§]	X*√[18,§]

√ = indicated; X = not indicated.
* FDA-approved Prescribing Information.
† Felbamate is not indicated for first-line use.
‡ Supported by randomized, controlled clinical trials.
§ Supported by open-label studies and/or anecdotal evidence.
‖ Can be effective in myoclonic astatic epilepsy[13].

Table 2. Pharmacokinetics of newer antiepileptic drugs[4,15,18,23,37,38,41,43–48,51,52]

AED	Absorption	Protein Bound	Metabolic/ Elimination Route	Mean $t_{½}$ (h)	Mean T_{max} (h)	Drug Interactions	Therapeutic Range (µm/mL)
Felbamate	> 90%	22%–25%	50% hepatic[37]; 50% renally excreted unchanged	20–23	2–6[18]	Clearance increased by enzyme inducers and decreased by valproate; increases phenytoin, phenobarbital, and valproate levels and decreases carbamazepine levels; reduces OCP effect	40–100 µg/mL[18]
Gabapentin	Saturable and dose-dependent	< 3%	17% hepatic; 77%–100% renal[4,15,18]	5–7*	2–3[18]	Virtually none	5–10[18]
Lamotrigine	98%	55%	90% hepatic glucuronidation[4,38]	12.6	1.4–4.8	C_{max} decreased by enzyme inducers and increased by valproate; serum levels decreased by OCP, rifampin; may reduce OCP effect; autoinduction can reduce $t_{½}$ 25%	1–20[18]
Levetiracetam	Almost 100%	< 10%	24% nonhepatic hydrolysis; 66% renally excreted unchanged	7 ± 1*(adult)	1–4[18]; increased by 1½ h when taken w/ food*	None	Not established[18]
Oxcarbazepine	100%	40% (active metabolite)	70% hepatic[4]; 95% renal excretion	4–9[18,38,*] (active metabolite)	4.5 (median)	Can inhibit CYP2C19 and induce CYP3A4/5; levels decreased by carbamazepine, phenytoin, valproate, verapamil; phenytoin levels increased 40%; reduces OCP effect; decreases felodipine levels	30–200 (active metabolite)[18]
Pregabalin	≥ 90%	0%	90% renally excreted unchanged	6.3	≤ 1.5	None	Not established
Tiagabine	Approaching 100%[18]	96%	98% hepatic[4] (mostly CYP3A)	7–9*	0.5–2[18]	$t_{½}$ decreased by 50%–65% by enzyme inducers[15]; potential protein-binding displacement	Not established[18]
Topiramate	≈80%	15%–41%	≈70% renally excreted unchanged	21	≈2	Serum levels decreased 40%–48% by enzyme inducers; can reduce OCP effect; potentially increases phenytoin; decreases lithium, digoxin levels	2–20[18]
Zonisamide	Approaching 100%[18]	≈40%	70% hepatic[4] (CYP3A4)	≈63	2–6; 4–6 if taken w/food	Concentration altered by drugs that induce or inhibit CYP3A4; $t_{½}$ decreased to 27 h by phenytoin, 38 h by carbamazepine and phenobarbital, 46 h by valproate	10–30[18]

* Pharmacodynamic action at receptor site outlasts $t_{½}$[16].
OCP = oral contraceptive pills.

instruction and follow-up appointment with the treating physician should be provided at the time of discharge from the ED.

Breakthrough seizures in the ED

Despite advances in antiseizure therapies over the past decade, emergency physicians still encounter a patient presenting in an ED after a breakthrough seizure. How often this occurs is difficult to say as there are no recent reports that quantify ED utilization for the management of breakthrough seizures. However, data from a recent review of records completed by the CDC's National Center for Health Statistics indicate that there were 83,000 ED visits for breakthrough seizures in 2004[10]. Regardless of the prevalence, a breakthrough seizure is a clinically significant event that requires comprehensive evaluation, often in coordination with a consulting neurologist.

Breakthrough seizures are often a consequence of sub-therapeutic AED levels. This may be caused by poor adherence; sub-therapeutic dose of antiseizure

Table 3. Adverse effects of newer antiepileptic drugs[15,18,23,38,43–48,51,52]

AED	Common Nonserious Adverse Effects	Serious Adverse Effects
Felbamate	Adults: anorexia, vomiting, insomnia, nausea, dizziness, somnolence, headache Pediatric: anorexia, vomiting, insomnia, headache, somnolence	Aplastic anemia, hepatic failure
Gabapentin	Weight gain; peripheral edema; behavioral changes, especially in children[38] Adults: somnolence, dizziness, ataxia, fatigue, nystagmus Pediatric: viral infection, fever, nausea and/or vomiting, somnolence, hostility	Irritability in cognitively impaired patients[18]
Lamotrigine	Tics, especially in children Adults: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, rash, coordination abnormality, dyspepsia, rhinitis, anxiety, insomnia, infection, pain, weight loss, chest pain, dysmenorrhea Pediatric: infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, diplopia, insomnia[38]	Rash possibly progressing to Stevens-Johnson syndrome; toxic epidermal necrolysis; diplopia[15]; hypersensitivity reactions, including renal or hepatic failure, DIC, arthritis[38]
Levetiracetam	General cognitive effects: fatigue, coordination difficulties; anxiety; agitation; psychotic symptoms Adults: somnolence, asthenia, infection, dizziness, irritability, insomnia, ataxia, tremor, headache, nausea, behavioral abnormalities Pediatric: somnolence, hostility, nervousness, asthenia, behavioral abnormalities	None
Oxcarbazepine	Dizziness, somnolence, fatigue, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait, possible weight gain[23], diplopia, nausea[15], headache[23] General cognitive effects: psychomotor slowing, difficulty with concentration, speech or language problems	Rash possibly progressing to Stevens-Johnson syndrome; toxic epidermal necrolysis; hyponatremia, especially in older patients[38]
Pregabalin	Dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, difficulty with concentration or attention	Male-mediated teratogenicity, ophthalmologic changes, elevated creatine kinase levels
Tiagabine	Dizziness, asthenia, nausea, irritability, tremor, abdominal pain, somnolence, fatigue, confusion, impaired concentration, speech or language problems, nervousness, depression	Nonconvulsive status epilepticus[15], stupor or spike wave stupor[38], moderately severe to incapacitating weakness, serious rash, exacerbation of spike/wave discharges associated with cognitive/neuropsychiatric events
Topiramate	Metabolic acidosis, paresthesia, weight loss, somnolence[18], anorexia[15], dizziness, ataxia, nausea[23] General cognitive effects: confusion, psychomotor slowing, difficulty with concentration, speech or language problems; depression; fatigue; difficulty with memory	Acute myopia associated with secondary angle closure glaucoma (rare)[15]; hypohidrosis[38], oligohidrosis, or hyperpyrexia (especially in pediatric patients)[15]; kidney stones; depression[23]
Zonisamide	Somnolence, anorexia, dizziness, headache, nausea, agitation/irritability, depression, psychomotor slowing, difficulty with concentration, speech or language problems, fatigue, photosensitivity, weight loss[38]	Rash possibly progressing to Stevens-Johnson syndrome, hypohidrosis[38], oligohidrosis or hyperpyrexia in pediatric patients, kidney stones, psychosis

Table 4. Precautions or warnings for newer antiepileptic drugs[20,26,38,43–48,51,52,*]

AED	Precautions or Warnings
Felbamate	Use carries risk of fatal aplastic anemia or hepatic failure; patients with blood dyscrasia, hepatic function disorder, or collagen-vascular disorders[26] should avoid use
Gabapentin	Patients with significant renal impairment or those on hemodialysis require dose adjustments
Lamotrigine	Patients with significant hepatic or renal impairment require dose adjustments; patients with collagen-vascular disorders in the first trimester of pregnancy[20] should avoid use; patients taking the drug in combination with valproate should discontinue its use at the first sign of rash
Levetiracetam	Patients with significant renal impairment or hemodialysis require dose adjustments
Oxcarbazepine	Patients with significant hepatic or renal impairment require dose adjustments; patients with a history of hypersensitivity reaction to carbamazepine should discontinue its use at the first sign of rash
Pregabalin	Patients with significant renal impairment or hemodialysis require dose adjustments; weight gain or peripheral edema in patients with diabetes can be clinically significant
Tiagabine	Patients with significant hepatic impairment require dose adjustments; use carries risk of causing status epilepticus
Topiramate	Patients with significant renal impairment or hemodialysis require dose adjustments; metabolic acidosis, especially in patients with bicarbonate-lowering condition, can be clinically significant; use of concomitant valproate carries risk of hyperammonemia and encephalopathy
Zonisamide	Patients with significant hepatic or renal impairment require dose adjustments; potentially fatal reaction can occur when concomitant sulfonamides are administered; discontinue use with first sign of rash

* As a class, all AEDs are listed as Category C for pregnancy and should only be prescribed if the benefits justify the potential risks.

medication; pharmacokinetic interactions of/with certain newly initiated concomitant drugs; and recent substitution of a generic AED for a brand AED.

Poor adherence is the most common cause of breakthrough seizures. Non-adherence, especially among patients with financial limitations, can be due to economic concerns such as the cost of the drug or

the cost of an office visit to renew a prescription[11]. Another cause for non-adherence can be the difficulty of accepting a diagnosis of a chronic condition such as epilepsy, especially for children and adolescents[11]. Unpleasant adverse drug effects, often cosmetic or cognitive, are also a threat to adherence[12].

A patient may also experience a breakthrough seizure because of sub-therapeutic AED levels when the prescribed dose is insufficient to provide seizure control[11]. Unlike established therapeutic ranges for older AEDs that can be applied to most patients, therapeutic levels for newer AEDs are less well defined. The management rule with these AEDs is to treat the seizure, or the clinical response, and not the serum levels[9,11,13].

Initiation of a new medication or ingestion of certain over-the-counter (OTC) products can reduce the bioavailability of an orally administered AED, increasing the risk of a breakthrough seizure. For example, gastric absorption of phenytoin can be significantly impaired when taken with antacids[14]. Drugs or other agents that induce cytochrome P450 enzymes can enhance the clearance of phenytoin and carbamazepine, which are extensively metabolized by these oxidative enzymes. In addition, carbamazepine – and to a lesser extent phenytoin in some patients – can cause auto-induction of P450 enzymes early in the course of therapy[15–17].

For older AEDs, which have a narrow therapeutic window, generic substitution can lead to breakthrough seizures or dose-related toxicities[18,19]. This is because of variations in the bioavailability of various generic formulations, which can be anywhere from 80% to 125% of the bioavailability of the brand drug[18,20].

Breakthrough seizures may also be a consequence of inadequate seizure control caused by prescription of an inappropriate AED because of misdiagnosis of seizure syndrome; exacerbation of certain seizure syndromes by prescription of inappropriate AED; progressive decline of some seizure syndromes; presence of precipitating factors that lower a patient's seizure threshold; and disease-related changes that require an increase in AED dose or an adjunctive AED.

Because idiopathic generalized epilepsies (IGE) can be difficult to diagnose[21], an inappropriate AED may be prescribed, resulting in breakthrough seizures. Caused by a genetically determined low seizure threshold, generalized epilepsies are often diagnosed by characteristic epileptiform abnormalities on electroencephalograph (EEG) tracings[21].

Although difficult to diagnose, many patients with an IGE syndrome are well controlled when appropriately treated[22]. Thus, many treatment failures for IGE are due to an inaccurate diagnosis of the syndrome[9] and/or treatment with an inappropriate AED, such as phenytoin or carbamazepine[11,21]. In addition, seizure control of some IGE syndromes can be worsened or exacerbated by some AEDs[15,21,23,24].

Various subtypes of IGE seizures that may be aggravated by AEDs include absence epilepsy (phenytoin, carbamazepine, oxcarbazepine, tiagabine, gabapentin, and pregabalin), atypical absence epilepsy (lamotrigine), myoclonic epilepsy (phenytoin, carbamazepine, oxcarbazepine, tiagabine, lamotrigine, gabapentin, and pregabalin), juvenile myoclonic epilepsy (lamotrigine in a small subset of patients), tonic epilepsy (carbamazepine and oxcarbazepine), generalized tonic-clonic epilepsy (tiagabine), and atonic epilepsy (phenytoin, carbamazepine, and oxcarbazepine)[15,21–24].

Partial onset epilepsies, on the other hand, may be caused by a focal structural defect in the cerebrum that can usually be detected with magnetic resonance imaging (MRI)[18]. However, some forms of partial epilepsy become more difficult to control over time. Although the idea that epilepsy itself is epileptogenic ('seizures beget seizures') has fallen out of favor[3], it is clear that some common forms of partial onset epilepsy, such as mesial temporal lobe epilepsy with hippocampal sclerosis, are progressive and can become more difficult to control over time[25].

Several precipitating factors that lower an epileptic patient's seizure threshold can trigger breakthrough seizures[9,19,26].

- Alcohol consumption.
- Sleep deprivation.
- Emotional stress.
- Exercise.
- Use of stimulants.
- Intercurrent illness.
- Toxic condition or metabolic abnormality.
- Pregnancy or other events that change ovarian hormone levels.

All types of epilepsy – but especially generalized epilepsies, such as juvenile myoclonic epilepsy – are sensitive to alcohol intake and/or sleep deprivation[9,26].

Various stimulants have a proconvulsant effect. The list includes illicit drugs such as amphetamines, cocaine, or methylenedioxymethamphetamine (MDMA, also known as *ecstasy*). Seizure threshold can also be reduced by certain prescription drugs, such as bupropion, tramadol, albuterol, tricyclic antidepressants, sympathomimetic drugs, and anticholinergic drugs. Additionally, OTC diet or cold and allergy preparations that contain pseudoephedrine or phenylpropanolamine, herbal products containing ma huang, and excessive caffeine consumption can also lower the threshold[19,26,27].

An intercurrent illness, such as a systemic infection and/or fever, can lower one's seizure threshold, as can various toxic conditions or metabolic abnormalities including hyponatremia, hypo- or hyperglycemia, hypocalcemia, hypoxia, hepatic encephalopathy, uremia, or pre-eclampsia/eclampsia[19,27].

Because estrogen is epileptogenic and progesterone has an opposing antiseizure effect, any changes in the absolute or relative levels of estrogen and progesterone can trigger a breakthrough seizure[1]. This may be seen during the menstrual cycle (catemenial epilepsy)[28], during pregnancy, and during perimenopause. In the case of lamotrigine, initiation of OCPs can lower lamotrigine serum levels, which can result in breakthrough seizures. Pregnancy can also cause a breakthrough seizure due to altered absorption, an increased renal clearance of AEDs excreted via kidneys, clearance of highly protein-bound AEDs caused by decreased serum albumin and subsequent protein binding, or other changes in volume of distribution that can lower AED blood levels[19,27,29].

Patient management and information gathering

The first rule in ED management is to stabilize the patient, providing interventions to stop an ongoing seizure[30]. Status epilepticus is a medical emergency; intervention with an IV anticonvulsant should occur within 5 min of onset of seizure[7]. Similarly, a patient experiencing a flurry of complex partial or primarily or secondarily generalized seizures should be stabilized with an IV anticonvulsant[7]. A patient who has experienced an aura (the hallmark of a simple partial seizure) may require immediate intervention to prevent progression to a secondarily generalized seizure[31].

During the initial screening, it is important to remember that even patients with epilepsy can have a non-epileptic seizure event – perhaps caused by cardiac arrhythmia, syncope, or dystonia – that requires emergency management[1,27]. For example, if the breakthrough seizure was caused by eclampsia in a pregnant woman close to term, delivery of the fetus should be considered[19].

One should check for physical injury or trauma that may have been sustained because of loss of consciousness or during a convulsive seizure. In the postictal period following a convulsive or non-convulsive seizure, a patient can be dazed for several hours and physically weak for days. Following a generalized tonic–clonic seizure, serum bicarbonate levels are often reduced because of transient lactic acidosis[32]. Persistent impairment in mental status, however, should be addressed with a determination of oxygenation and serum glucose and consideration of obtaining an electroencephalograph (EEG) to assess for non-convulsive status epilepticus[19,27,30].

Once the patient is stable, the steps to determine if the patient has experienced a breakthrough seizure and the underlying cause are to obtain medical and social history; determine seizure history from patient and witness (if available); conduct physical examination, including neurologic exam; and consider diagnostic tests, depending on history and physical-exam findings.

A thorough medical, social, and seizure history should be obtained from both the patient and the witness of the seizure[27]. A description of the patient's behavior before, during, and immediately after the seizure can help determine if it was a primarily generalized or partial onset seizure. Considerations that will help in the classification include duration of the seizure, whether an aura was present, whether consciousness was lost or impaired, whether the patient displayed involuntary automatic movements (e.g., tongue biting or urinary incontinence), and the type of involuntary muscle contractions.

Focal, or partial onset, seizures are classified as either simple (no loss of consciousness) or complex (consciousness is impaired or lost during the seizure). Simple partial seizures are characterized by an aura that can have a variety of presentations, including sensory (e.g., an unexplained smell or sound), physical (e.g., an unpleasant abdominal sensation), emotional (e.g., fear, sadness, depersonalization), or psychic (e.g., *déjà vu*) sensations, depending on the location of the focal defect. A complex partial seizure may or may not begin as an aura, but it is always characterized by altered awareness, unfocused staring, automatic, involuntary movements, and loss of memory of the seizure[19]. Both simple and complex partial seizures can evolve into secondarily generalized seizures, which can be difficult to distinguish from generalized tonic–clonic seizures[19].

Generalized epilepsy can manifest as:

- Absence seizures: a frequent, subtle, brief (≈5–15 s), unfocused staring or a lapse in consciousness without a preceding aura or postictal state.
- Tonic–clonic seizures: a stiffening of the body followed by violent jerking of arms and legs and loss of consciousness lasting approximately 50–90 s.
- Myoclonic seizures: sporadic, brief, superfast jerks of the limbs that are usually symmetrical.
- Clonic seizures: relatively rare seizures in which there are jerking contractions without a preceding tonic phase.
- Atonic seizures: short periods of tone loss that can range from a slight drop of the head to total collapse (drop attack).

- Tonic seizures: muscle contractions that are more sustained than in myoclonic seizures without periods of relaxation[18,21].

Combinations of multiple seizure types are referred to as seizure syndromes; the most recognized include juvenile myoclonic epilepsy, Lennox–Gastaut syndrome, and Unverricht–Lundborg disease.

A patient's history should include co-morbid conditions and concomitant medications, including OTC preparations and herbal supplements, which can play a significant role in breakthrough seizures. Information about a patient's personal life and social behaviors, such as recent stressful events or a history of alcoholism or illicit-drug use, can provide important clues[33].

A physical examination should include vital signs, a search for signs of acute trauma, and a funduscopic exam and assessment of nuchal rigidity to detect signs of increased intracranial pressure or CNS infection, respectively[27]. A neurologic examination should be conducted for signs of focal neurologic defects, such as Todd paralysis[27]. Clinical laboratory tests should include a complete blood count and differential, electrolytes, serum glucose, calcium, and magnesium levels. When suggested by a patient's history or physical-examination findings, certain tests – renal or liver function, a urinary analysis, a toxicology screen, or a pregnancy test for women of childbearing age – should be added[27].

Obtaining serum AED levels may be useful, taking into consideration the last time the patient ate, timing of the last dose, the patient's general health status that might lower AED levels (e.g., vomiting or diarrhea), and if the AED was recently initiated (not yet at steady–state)[32,34]. A normal total AED level may be misinterpreted as adequate when there is an elevated serum protein level, which can occur with pregnancy or severe alcoholism. In these cases, AEDs that are highly protein-bound, such as phenytoin, valproate, and tiagabine, may have lower levels of free AED. As stated earlier, AED serum levels should be considered a clinical tool, but not an absolute determinant of therapeutic status. Standard therapeutic ranges of AEDs do not necessarily apply to every individual, even with older AEDs for which those ranges are well established[11,13]. Please see Figure 1, a flow chart of assessments to be conducted in the ED of a patient who has epilepsy with breakthrough seizure.

Neurology consultation

The decision to make an adjustment to an AED regimen, such as increasing the frequency of dosing or adding an adjunctive AED, should be made in coordination with a consulting neurologist[35]. Fortunately, many EDs have rapid access to a neurologic consult, which can be very

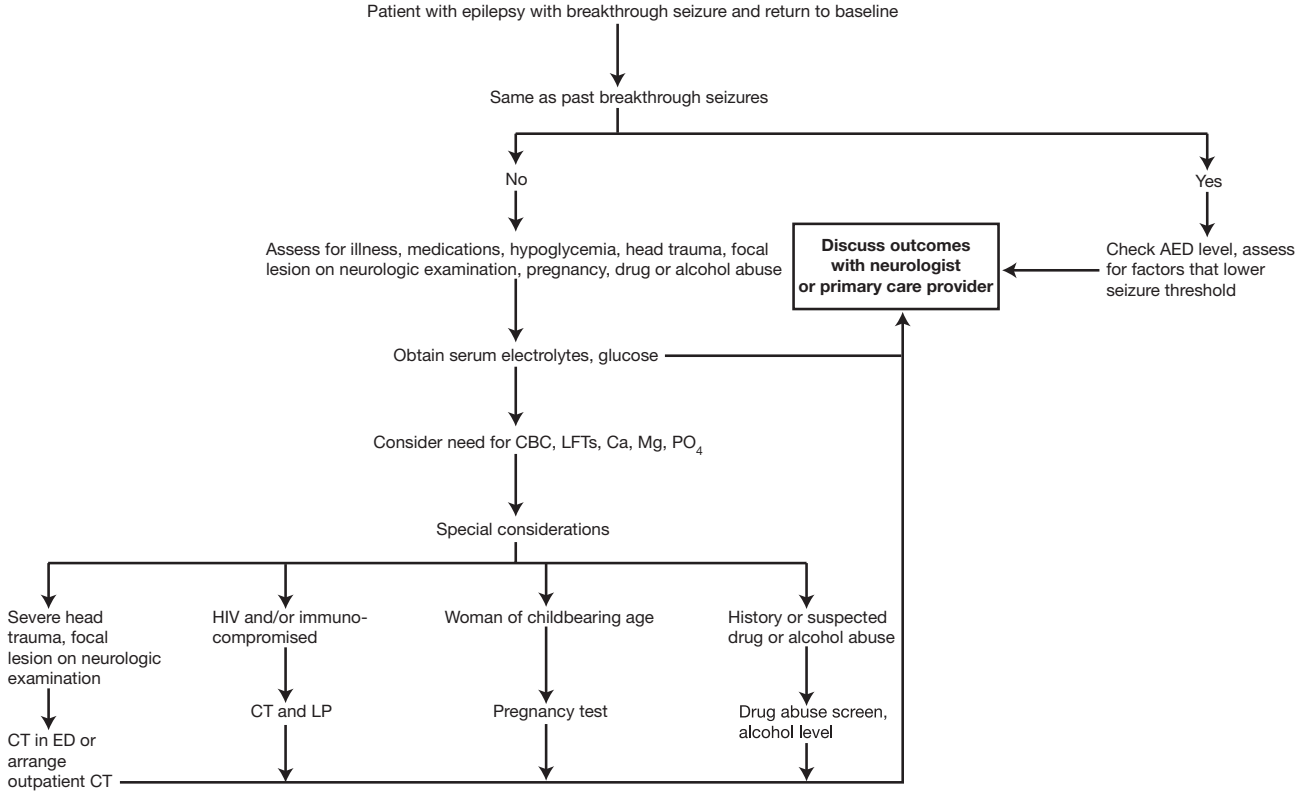

Figure 1. *ED assessment of a patient with epilepsy with breakthrough seizure*

helpful in deciding when and how to make adjustments to a patient's antiseizure regimen[35]. When approaching a neurologist, be prepared to discuss details of the breakthrough seizure, clinically significant findings, co-morbid conditions, and concomitant medications, as well as any outstanding features, such as extremes in body weight and mental or behavioral disturbances, e.g., clinical depression or extreme irritability[7].

Key information for a neurology consultation about a patient who has experienced breakthrough seizure:

- Type of epilepsy.
- Duration of breakthrough seizure.
- Whether patient has returned to baseline status.
- Recent onset of new medical conditions, including trauma.
- Whether patient is pregnant.
- Recent initiation of new medications.
- Generic substitution of AED.
- Recent drug use, including alcohol, caffeine, OTC cold preparations, and herbal remedies.
- Serum AED level, if available.
- Physical, neurologic, and behavioral status of the patient.

Disposition of the patient

Be sure to check the terms of a patient's healthcare insurance before issuing a new prescription, because some insurance carriers will not reimburse the cost of AED therapy if prior authorization is not obtained. If prior authorization is required, this should be mentioned in the chart notes that will be forwarded to the patient's PCP/neurologist. Partial or full IV or oral loading may be indicated if the older AED serum level is significantly below the desired level for the individual patient[19,27,34]. Among the eight newer AEDs available as oral formulations, only levetiracetam is also available in an IV formulation. The choice of AED, made by the consulting neurologist, is guided by the seizure type or syndrome; but if for some reason there is doubt as to which AED to add, consider using one of the newer broad-spectrum AEDs: lamotrigine, levetiracetam, topiramate, or zonisamide[21–23,36,37].

Comparative overview of older and newer AEDs

As a class, older AEDs are associated with complex pharmacokinetics and undesirable side effects that can play a causative role in breakthrough seizures[7,9,12,26,38,39]. Phenytoin has zero-order, nonlinear kinetics at therapeutically relevant doses, and variable dose-to-serum ratios for many patients[4,8]. Both phenytoin and valproic acid are highly protein bound, so their clearance can be increased because of displacement from their binding sites by competing drugs or low serum albumin.

Phenytoin and carbamazepine are potent inducers of P450 enzymes, increasing the clearance of commonly prescribed drugs such as oral contraceptives, calcium channel blockers, warfarin, chemotherapeutic agents, statins, antidepressants, and antibiotics[7,38]. The induction of P450 enzymes increases the metabolism of sex steroids, resulting in reproductive disorders and the metabolism of vitamin D, which can lead to significant depletion of bone mineral[7,40]. These enzyme inducers are also associated with increased levels of homocysteine, which has been linked to coronary artery, cerebrovascular, or small-vessel disease[7]. On the other hand, valproic acid is a potent inhibitor of P450 enzymes, causing drug interactions with concomitant AEDs and other classes of drugs and disruption of the hormonal milieu[38].

Since 1993, the FDA has approved 10 new AEDs[15,38]. While each new AED has unique features and limitations, as a group, these newer AEDs have antiseizure efficacy comparable to the older AEDs with better tolerability, fewer drug interactions, and less effect on cognitive functions[9,39]. Because they generally have fewer drug interactions and milder AEs, the newer AEDs increase the possibility of patient adherence and thus seizure control[11].

Of the oral AEDs available in the United States, the commonly used older AEDs include carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid. The oral AEDs introduced since 1993 are divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide.

Of the parenteral AEDs available in the United States, the commonly used older AEDs include diazepam, phenobarbital, and phenytoin. The parenteral AEDs introduced since 1993 are fosphenytoin, levetiracetam, and valproate. See the accompanying tables, listing the indications (Table 1), pharmacokinetic features (Table 2), notable side effects (Table 3), and precautions or warnings (Table 4) of the newer oral AEDs.

When choosing a dose for reinstitution of an AED, some of the newer AEDs have specific pharmacokinetic considerations:

- Levetiracetam can be reinstituted at the previous daily dose, with half of the dose given twice daily.

- Re-initiation of oxcarbazepine can be done more rapidly than can the initial titration regimen, starting at the low therapeutic dose of 300 mg b.i.d.
- Tiagabine has a longer pharmacodynamic effect than half-life, so re-initiation should be done at the low end of the therapeutic dose.
- Loading doses or rapid titration should be avoided with tiagabine.
- Topiramate should also be titrated slowly to avoid intolerable cognitive AEs.
- Although the therapeutic dose for zonisamide is 200–400 mg/day, its half-life is about 60 h, so a starting dose should not be more than 100 mg/day to avoid significant sedation.

In addition to recommending changes in AED regimen, you should advise patients of precautions they should take until their seizure disorder has stabilized. Chart notes should indicate that patients and/or their family members have been advised of and understand these precautions. This includes state regulations on driving motorized vehicles and operating heavy machinery and caveats concerning swimming or bathing alone, climbing ladders, using power tools, or cooking alone.

Referral to the treating physician

Continuity of patient care requires comprehensive communication between the ED and the patient's treating physician[19,35]. Notification that a patient has been seen in the ED for a breakthrough seizure, any significant findings during the ED visit, and any treatments or changes in AED regimen should be communicated to the treating physician, with whom a follow-up appointment should be scheduled[35]. When changes are made to an AED regimen, a call should be made before discharge from the ED to the treating neurologist or physician to schedule a follow-up evaluation, generally within 2–3 weeks. If the breakthrough seizure was due to non-adherence, underlying reasons for non-adherence (such as undesirable side effects) should be communicated to the treating physician. If non-adherence is due to economic concerns, social services can play an important role in connecting patients with a pharmaceutical company-sponsored assistance program that can provide low-income uninsured patients with their AED medications. Social services can also conduct a home assessment if it is suspected the patient is living in a non-supportive environment[35].

Conclusions

On occasion, emergency physicians are the providers of medical care for breakthrough seizures. Determining the underlying cause requires a comprehensive evaluation of the patient. Because of the complexities of AED therapies, any adjustments to an AED regimen should be made in coordination with a consulting neurologist. The primary goal in the ED is to stabilize the patient, and the primary goal of AED therapy is to provide freedom from seizures without side effects. A neurology consultation can assist emergency physicians in choosing an AED that may contribute to greater adherence and thus better seizure control. Emergency physicians should also seek to preserve continuity of patient care with effective communication and coordination with a patient's treating physician.

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