Breakthrough Seizures—Approach to Prevention and Diagnosis

an expert interview with

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Q: Why is there a need to focus on breakthrough seizures?

A: When an epilepsy patient experiences a sustained period of freedom from seizures (seizure control), then suddenly experiences a seizure, such an event is commonly referred to as a breakthrough seizure. When these breakthrough seizures occur, there can be severe clinical consequences for the patient. For example, patients may need to be examined in a hospital or evaluated in the emergency room. Sometimes fractures or head injuries may occur, which could warrant hospitalization. Cases in which a breakthrough seizure evolves into a ongoing seizure state, or 'status epilepticus,' require a well-established series of life-saving interventions, including assessment of airway and vital signs, establishment of intravenous access, blood testing, and loading of antiepileptic medications to try to stop the seizure state. This is very important as status epilepticus is associated with elevated morbidity and, potentially, mortality.

Breakthrough seizures have their own unique set of potential etiologies that should be carefully considered by the clinician, as I will discuss later.

What causes breakthrough seizures?

There are a number of potential causes of the unexpected occurrence of a breakthrough seizure. One important factor that clinicians may forget to examine is the possibility of non-adherence to (non-compliance with) prescribed antiepileptic drugs (AEDs). While adherence to medication is important in all disorders, it is especially important in epilepsy as non-adherence can lead to the emergence of breakthrough seizures and all of the associated complications. When assessing the causes of a breakthrough seizure, the clinician must first establish whether the patient in question has been adherent to the prescribed AEDs.

Both patient and medication factors can contribute to the occurrence of a breakthrough seizure. Patient factors include the onset of an infection, severe emotional stress, sleep deprivation, or metabolic events such as a decrease in sodium levels or severe changes in blood sugar level. Provocative factors such as flashing lights or playing video games have also been known to induce a seizure. A drop in serum AED level can provoke a seizure, and there are diverse potential causes for a reduced level. For example, the introduction of an agent that induces hepatic metabolism can lower the level of some AEDs metabolized in the liver, leading to higher risk for a seizure. There are also certain medications that are known to lower the seizure threshold, and the addition of such an agent would certainly predispose patients to a breakthrough seizure; a comprehensive list of factors is presented in *Table 1*. Other possibilities include the discontinuation or tapering of an AED, which could lead to potential withdrawal seizures. Paradoxically, there have been rare cases in which elevation of AED levels have induced seizures as well. For example, this has been described in the case of phenytoin toxicity. Sometimes, specific causes cannot be identified other than the manifestation of the underlying epileptic disorder.

What are the factors leading to loss of adherence to or discontinuation of antiepileptic drug therapy?

There are many potential causes of non-adherence in epilepsy. Adverse effects such as cognitive dysfunction or fatigue are commonly associated with use of AEDs, and the occurrence of these events may compel patients to take less of their medication—sometimes without even notifying their physician. Other adverse effects could include weight gain or sexual dysfunction—topics that patients may be disinclined to discuss. Complexity in the dosing regimen may contribute to the problem. For example, large numbers of pills that need to be ingested, different doses at varying times of the day, or how often a patient has to stop his or her daily routine to self-medicate can all potentially reduce adherence. Language barriers can also hinder the clinician's ability to effectively convey the importance of adherence and dosing instructions to the patient. A patient's lack of familiarity with his or her prescription plans and insurance issues can also play a role.

Forgetting to take a medication also contributes to non-adherence, and although this can happen to anyone (including clinicians), it can have

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potentially devastating ramifications for patients with epilepsy. There is also a chance that patients simply do not fully understand the nature of the treatment and the importance of remaining adherent; if a patient happens to have a long period in which he or she is seizure-free in the face of non-adherence, that patient may be lulled into a false sense of confidence that skipping medications will have minimal consequences.

What are the consequences associated with breakthrough seizures related to non-adherence?

In addition to the risk for injury requiring hospitalization and monitoring, there are significant effects on economic costs and mortality. We utilized data from the Integrated Health Care Information Services in a retrospective analysis examining the prevalence and cost impact of non-adherence in an elderly population aged 65 years and over with epilepsy.[1] Adherence was evaluated using the medication possession ratio (MPR), a standard accepted analysis tool that estimates the ratio of total days supplied of a medication over the days between AED refills. An MPR ratio greater than or equal to 0.8 is traditionally used as the cut-off designating good adherence, with a ratio lower than 0.8 as non-adherence. The results of the study were very worrying, in that nearly 41% of the patients studied had an MPR ratio less than 0.8—meaning that virtually half of the patient population had poor adherence. This non-adherence was also strongly correlated to the occurrence of serious seizures, which led to an overall increase in the number of visits to the physician's office, emergency department, and hospital. There was also a substantial increase in the risk for hospitalization, which resulted in escalated costs of approximately $2,400 per patient as a result of the additional interventions that were needed because of non-adherence. These statistics may even be an under-representation of the problems associated with suboptimal adherence in epilepsy patients, because it is conceivable that some patients, even in the face of a major seizure, did not seek additional care from hospitals.

The risks associated with AED non-adherence have also been graphically demonstrated in the recently published Research on Antiepileptic Non-adherence and Selected Outcomes in Medicaid (RANSOM) study.[2] This retrospective examination of Medicaid data studied the AED adherence of epilepsy patients aged 18 years and over utilizing the MPR, and found an association between periods of non-adherence and significantly higher incidence of visits to emergency departments, hospitalizations, fractures, and injuries related to motor vehicle accidents compared with periods of adherence. Furthermore, patients non-adherent to AEDs exhibited a three-fold increased risk for mortality compared with adherent patients.

What would you recommend in order to reduce the occurrence of breakthrough seizures?

It is intuitive that the selection of an AED would be based primarily on efficacy, and many of the available agents are quite comparable in their efficacy. However, there are other factors that the clinician should consider when selecting the optimal AED, such as potential side effects, ease and frequency of administration, cost-effectiveness, and drug interactions. I would encourage any clinician prescribing an AED to review the side effects commonly associated with AEDs overall, as well as the potential side effects specific to each individual agent being considered. By familiarizing themselves with the drug information, clinicians will be better able to review the drug characteristics with the patient and warn of potential side effects, as well as the need to contact the physician before autonomously discontinuing the medication.

Table 1: Drugs That May Lower the Seizure Threshold

Category	Drug
Antiasthmatics	Aminophylline
	Theophylline
Antibiotics	Isoniazid
	Lindane
	Metronidazole
	Nalidixic acid
	Penicillins
Antidepressants	Bupropion
	Tricyclics
	Serotonin-specific agents
General anesthetics	Enfluraneketamine
Hormones	Estrogen
	Insulin
	Oxytocin
	Prednisone
Immunosuppressants	Chlorambucil
	Cyclosporine a
Local anesthetics	Bupivicaine
	Lidocaine
	Procaine
Narcotics	Fentanyl
	Meperidine
	Pentazocine
	Propoxyphene
Psychostimulants	Amphetamines
	Cocaine
	Methylphenidate
	Phenylpropanolamine
Neuroleptics	Clozapine
	Butyrophenones
	Phenothiazines
Other	Anticholinergics
	Anticholinesterases
	Antihistamines
	Baclofen
	Heavy metals
	Hyperbaric oxygen
	Lithium
	Mefenamic acid
	Oral hypoglycemics

Adapted from Koppel BS, Contribution of drugs and drug interactions (prescribed, over the counter, and illicit) to seizures and epilepsy. In: Ettinger AB, Devinsky O (eds), Managing epilepsy and co-existing disorders, *Boston: Butterworth-Heinemann, 2002;155–173.*

In terms of reducing the occurrence of breakthrough seizures due to non-adherence, there are strategies that clinicians can use to improve patient adherence. Among these are greater efforts in promoting a better physician–patient relationship and taking the time to ensure that patients understand why the medications are required, what the nature of the dosing is, potential drug interactions, and possible side effects. Providing instructions and information in a written format can also be useful.

Communication obviously plays a big role. It is important to avoid the technical medical terms that we physicians are often inclined to use, and

Table 2: Patient Perception of Generic Antiepileptic Substitution

	Sample (n=974)	
Variable	Agree (%)	Disagree (%)
I am concerned about the safety of generic AEDs	66	32
I am concerned about the effectiveness of generic AEDs	68	31
The pharmacist should be able to substitute my AED for a generic medication only with the consent of my physician	88	12
I would be uncomfortable receiving a medication that was not specifically prescribed by my doctor	91	9
Cost should be a minor factor in selecting my epilepsy treatment	85	14
The effectiveness of my epilepsy treatment should be the primary concern when selecting a treatment	98	2
Substitution of your regular, effective AED can cause onset of breakthrough seizures that were previously controlled	72	22

Adapted from Haskins et al., 2005.[7] See reference for the complete survey.

Table 3: Physician Perception of Generic Antiepileptic Substitution

	Sample (n=974)	
Variable	Agree (%)	Disagree (%)
Substitution should not be allowed in certain indications where small differences in drug levels may adversely affect patient response	89	11
I am concerned about what may happen to my patients' epilepsy control as a result of generic AED substitution	68	32
I believe epilepsy is an example of a medical condition where the universal substitution of a branded medication with a generic without direct approval from a physician at the time of substitution is medically inappropriate and unacceptable	70	30
I believe the universal substitution of a branded AED medication with a generic without direct supervision and approval of their physician may jeopardize the seizure control and long-term health of some patients	74	26
I am concerned about an increase in breakthrough seizures in my patients who are switched from a branded AED to a generic (without dose increases)	69	31
Generic substitution of my controlled patients' regular, effective AED may cause onset of breakthough seizures	74	26
Allowing or enforcing generic substitution without my consent is dangerous because of the potential impact on patient welfare	76	23
Finding the right dose of the optimal treatment to prevent seizures is a complex and sometimes lengthy process	96	4

Adapted from Haskins et al., 2005.[7] See reference for the complete survey.

to use simpler layman terms instead. I often use the 'talkback technique' in order to break down confusing concepts into simple ideas: I provide the patient with instructions, then ask the patient to repeat back to me what he or she understands the nature of the treatment to be and what the dosing should be. The general concept here is one of promoting patient education and emphasizing the health consequences of poor AED adherence.

When there is concern about the risk for potential non-adherence in an individual case, follow-up phone calls can be used to ensure that the patient is taking his or her medications. Using pill boxes as an organizational tool may also help.

In additional to addressing patient adherence, there is an important and highly controversial ongoing debate concerning the substitution of branded drugs with generics. While it may be appealing to substitute a branded AED with a generic agent from a cost-cutting point of view, there are many potential concerns with doing this, largely around the topic of bioequivalence. Generic agents need to fall within a range of equivalence of 80–125% to the branded version before they receive US Food and Drug Administration (FDA) approval, and the substitution of a branded medication with a generic means that patients refilling their medication could potentially receive a different generic formulation each time. This variation in bioequivalence could therefore result in great differences in the effective drug level in the patient's bloodstream from one month to another, which could then result in a breakthrough seizure.

Similar sentiments have been expressed by the American Academy of Neurology and the Epilepsy Foundation, and recent studies appear to substantiate this concern[3–8] (see *Tables 2* and *3*). Patients who are switched to generics without their or their clinician's knowledge face a great disadvantage.

What is needed in future research and drug development to address breakthrough seizures?

I feel that research in this area needs to be catered toward the specific causes of breakthrough seizures. For example, in the case of adherence, further studies are needed to obtain a better understanding of the attitude and concerns of patients regarding their AEDs and what specific factors are interfering with their achievement of optimal AED adherence. Studies have shown that adherence is better if dosing is less frequent, hence the value of some extended-release formulations in promoting better adherence.[9] For drug interactions, rigorous studies are needed for each agent on its introduction to the drug regimen.

With regard to other central nervous system conditions that can lead to breakthrough seizures, there is much to be learned about the potential mechanisms by which these disorders can lead to seizures; through better understanding of these mechanisms, we will find ways to prevent the development of epilepsy. ■

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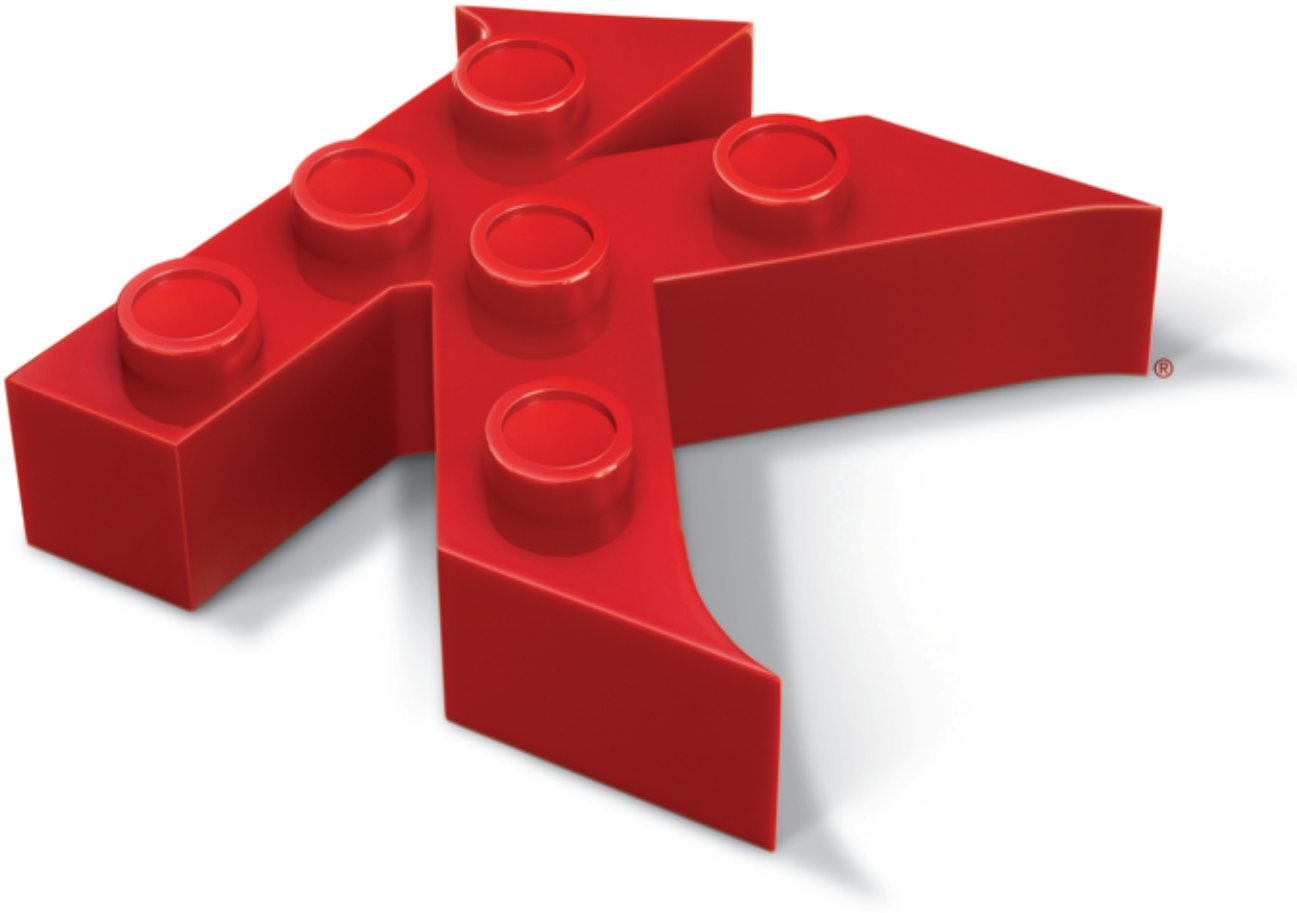

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