Optimizing Management of Medically Responsive Epilepsy

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ABSTRACT

PURPOSE OF REVIEW: **This article reviews the management of patients with medically responsive epilepsy, including discussion of factors that may lead to transient breakthrough seizures and patient and physician strategies to maintain freedom from seizures.**

RECENT FINDINGS: **Imperfect adherence, unanticipated changes in ongoing medical therapy, inadvertent use of proconvulsants or concurrent medications that alter epilepsy medication kinetics, and a variety of seizure precipitants such as stress or sleep deprivation may alter long-term seizure control.**

SUMMARY: **The majority of patients with epilepsy are medically responsive. Many potential factors may lead to breakthrough seizures in these patients. Identification of these factors, patient education, and use of self-management techniques including mindfulness therapy and cognitive-behavioral therapy may play a role in protecting patients with epilepsy against breakthrough seizures.**

INTRODUCTION

Much of the neurologist's attention in the evaluation and care of the patient with epilepsy is devoted to the goal of seizure remission. Continuing seizures confer higher risks of health care use, underemployment or unemployment, or sudden death. Once the hard work of seizure remission has succeeded, however, less attention is sometimes paid to staying seizure free. This article reviews the maintenance of patients with medically responsive epilepsy, including discussion of factors that may lead to transient breakthrough seizures and patient and physician strategies to maintain freedom from seizures.

DEFINITIONS AND INCIDENCE

Of the 50 million people worldwide and the 3.4 million people in the United States with epilepsy (roughly 1.2% of the population), two-thirds will become seizure free with appropriate pharmacotherapy.[1] Many of these patients will remain reliably seizure free, but some will have their daily routine interrupted by breakthrough seizures.

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RELATIONSHIP DISCLOSURE:
Dr Bauer is a site subinvestigator for GWEP-1521, a double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol as add-on therapy in patients with tuberous sclerosis complex who experience inadequately controlled seizures. Dr Quigg has received research/grant support as principal investigator of studies from the National Institutes of Health/National Institute of Neurological Disorders and Stroke, the University of Virginia Brain Institute, and ZETO Inc. Dr Quigg has received publishing royalties from Elsevier and has given expert medical testimony.

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KEY POINT

- Approximately two-thirds of patients with epilepsy will become seizure free with pharmacotherapy.

Breakthrough seizures—the primary topic of this article—must be distinguished from two other possibly confusing entities. First, reflex epilepsies are those in which seizures are provoked objectively and consistently by specific stimuli or activities in patients who otherwise lack spontaneous seizures.[2] For example, reading epilepsy does not fall into the scope of this review. Second, acute symptomatic seizures occur in patients with or without epilepsy and are provoked at the time of an acute, and usually severe, epileptic insult.[3] Examples of acute symptomatic seizures include those provoked by proconvulsant medications, illicit drug or alcohol withdrawal, traumatic head injury, or renal dialysis. Although the measures reviewed in this article may help susceptible individuals, the focus of this article is on maintaining seizure freedom (ie, avoidance of the breakthrough seizure) in a patient with known epilepsy.

A breakthrough seizure is defined as one that occurs despite the use of antiseizure medications that have otherwise successfully prevented seizures in the patient in the past. The duration of the seizure remission period (the minimum interseizure interval) needed to be considered seizure free varies with inherent seizure frequency. The International League Against Epilepsy (ILAE) defines *seizure free* or *medically responsive epilepsy* as seizure freedom for 12 months or 3 times the longest previous interseizure interval, whichever is longer.[4] This definition is handily referred to as "the rule of three."

Other studies define the durations of seizure remission differently. Later analyses with the use of Bayesian techniques suggests the "rule of three to six," whereby those with a high preintervention probability of seizure freedom should be without seizures for 3 times the previous interseizure interval prior to being considered seizure free, while those that have low preintervention probability of seizure freedom should wait up to 6 times the previous interseizure interval.[5]

Clinical research has varied from the ILAE definition of seizure freedom. For example, in a study of patients with seizures presenting to the emergency department, Divino and colleagues[6] defined breakthrough seizures as those that occurred more than 6 months from the previous seizure that were not clearly associated with antiseizure medication nonadherence. Alternatively, in a secondary analysis of a large comparison of new versus standard antiseizure medications, Bonnett and colleagues[7] required at least 12 months of seizure freedom for a recurrent seizure to be considered breakthrough. For the purposes of this review, seizure freedom follows the standard ILAE definition.

The estimated prevalence or incidence of breakthrough seizures varies widely by definition and sample. A Ugandan study estimated prevalence in a sample of 267 patients, of which 74% experienced breakthrough seizures; interseizure interval was not defined.[8] In an English sample of more than 2000 patients in a prospective, observational trial of standard versus newer antiepileptic drugs (the SANAD [Standard and New Antiepileptic Drugs] trial[9]), the investigators defined breakthrough seizures as those that recurred after at least 12 months of remission regardless of previous seizure frequency.[7] The incidence of breakthrough seizures was 37%.

CONSEQUENCES AND COSTS

As CASE 3-1 illustrates, breakthrough seizures can result in interruptions of schedules, potential injuries, or loss of work or driving privileges. Breakthrough seizures may place patients at worse risk because circumstances and activities are less restrained than those with continuing seizures. Seizures may result in motor

CASE 3-1

A 19-year-old woman presented to the emergency department for a generalized tonic-clonic seizure witnessed by her college roommate. She had a history of juvenile myoclonic epilepsy and had been seizure free on lamotrigine 100 mg 2 times a day from her junior year in high school (near the time of onset) to her second year in college (the time of her presentation to the emergency department).

She admitted to occasionally missing her lamotrigine morning dose, but she wasn't sure whether she had missed a dose on the day of this seizure.

Her medication had been recently refilled, and the generic pill she was accustomed to had changed manufacturers (and thus possible pharmacokinetic properties). She had also recently started oral contraceptives. Upon further questioning, she noted that she had just finished a term paper that had required relatively sleepless nights.

Because she presented with a head contusion from her seizure and was initially sleepy and disoriented after her seizure, she underwent a head CT, which was normal. Further laboratory testing in the emergency department showed that her lamotrigine level was 2 mcg/mL (lower limit of reference range >2.5 mcg/mL). During the neurology consultation in the emergency department, her gynecologist was contacted, and it was determined that she had been placed on a progesterone-only oral contraceptive, which was thought unlikely to be a contributing factor to low lamotrigine levels.

Given the patient's self-reported issues with adherence, her pharmacy was contacted. The patient filled her monthly lamotrigine prescription 9 times out of the prescribed 12 months. The medication possession ratio of 0.75 would suggest that she is missing the medication at least 25% of the time. Based upon this evidence, it was determined her seizure was most likely due to nonadherence. To address this, her lamotrigine was changed from 100 mg 2 times a day to 200 mg 1 time a day of the extended release formulation. In addition, she was counseled to maintain a regular sleep schedule.

Following the emergency department visit, she missed a day of classes and was prohibited from driving for 6 months.

COMMENT

This case illustrates an example of a breakthrough seizure. Breakthrough seizures interrupt a period of apparent seizure remission in a patient with known epilepsy. The costs in terms of injury, time, health care utilization, and employment can be considerable.

This case also displays the many factors that need to be considered with breakthrough seizures. Medication interactions, adherence, as well as the presence of possible seizure precipitants are all impediments to sustained seizure freedom. In this patient's case, the significance of her intermittent nonadherence was only made clear through discussion with her pharmacy. With adjustment of her antiseizure medication regimen to once-daily dosing, the patient was able to more reliably take her medication and once again achieved long-term seizure freedom.

vehicle injuries or other trauma. Breakthrough seizures may present as status epilepticus,[10] and higher rates of seizures and antiseizure medication nonadherence are associated with sudden unexpected death in epilepsy (SUDEP).[11] Economic costs follow trauma and morbidity. In a case-control study of those with breakthrough seizures, cases had significantly higher rates of hospitalization and emergency department visits compared with controls and higher total all-cause direct health care costs (median $12,714 versus $5095). All told, patients with breakthrough seizures had 2.3 times higher adjusted health care costs and 8.1 times higher adjusted epilepsy-related costs than controls.[6]

In the longitudinal management of patients with medically responsive epilepsy, the primary goal should be to maintain seizure freedom without side effects from antiseizure medication. The neurologist should be aware of the significant nonadherence issues inherent with chronic medication management, be vigilant for potential medication factors or interactions that can affect stable antiseizure medication kinetics, and identify common seizure precipitants. Management of these issues requires both physician expertise and buy-in from the patient.

An increasingly expanding body of literature exists regarding patient participation and empowerment in the long-term care of epilepsy, known as *self-management*, which is defined as "activities or steps that an individual or family can perform that are known to either control the frequency of seizures or promote the well-being of the person with seizures."[12] In other words, the maintenance of seizure freedom is best achieved when the physician and patient are reading from the same playbook.

RISK FACTORS FOR BREAKTHROUGH SEIZURES

Risks for breakthrough seizures have not been uniformly studied. In multivariate analyses of patients in the SANAD trial, three factors were found to be robust predictors of seizure recurrence: a history of neurologic insult defined as learning disability or a focal neurologic deficit resulting in functional impairment, the total number of tonic-clonic seizures recorded before achieving 12-month remission, and time taken to achieve 12-month remission.[7]

Although valuable for general prognosis of the potential and incidence of breakthrough seizures, the SANAD study, however, did not evaluate variables that could be modified by the physician or patient. Only two studies consisting of surveys of patients with breakthrough seizures have enumerated these factors in comparative fashion.[8,13] Both studies found that antiseizure medication adherence was the leading factor associated with breakthrough seizures (27% to 56%). Other factors fell into the broad category of seizure precipitants and will be discussed in the appropriate section below.

ADHERENCE

Treatment adherence is an important factor in maintenance of seizure control, and a gentle skepticism while taking a history of adherence helps both the physician and patient.

Prevalence and Measurements of Antiseizure Medication Adherence

Nonadherence is not confined to epilepsy. The World Health Organization estimates that medication nonadherence across all diseases is 50% worldwide.[14] Patients in US clinical drug trials for a variety of diseases demonstrate adherence

at rates ranging from 43% to 78%.[15] Despite being an endemic issue, the characterization of medication adherence, including in patients with epilepsy, is limited by lack of standardization in definitions and measurements.[15,16] For example, adherence may be characterized by dose adherence (ie, taking the proper number of pills of a medication in a given time interval) or by interval adherence (ie, taking medication in the prescribed intervals between doses). The most tangible example of dose adherence is pill count, which provides an objective measure of the number of pills taken over a period of time. Interval adherence may be assessed through patient diary or electronic monitoring technology. A practical adherence measurement in this area is the medication possession ratio, the ratio of total days with available medication to total days prescribed. A medication possession ratio of less than 0.8 is generally considered nonadherent.[16] This threshold translates to missing 3 doses a week in a twice-daily dosing regimen, which is an eye-opening rate to most physicians. Given this threshold, the proportion of patients who miss 3 or more doses per week ranges between 26% and 79%, with a suggested overall rate of 40%.[16]

Patients who are nonadherent may change patterns of nonadherence over time. Modi and colleagues[17] found that rather than fitting into a binary adherent or nonadherent paradigm, patients fell into four different patterns of adherence during long-term antiseizure medication therapy: high adherence, moderate adherence, severe early nonadherence, and variable nonadherence. In that study, 15% of patients displayed shifts among groups over the course of follow-up. Another clinically important example of variable adherence is so-called "white coat compliance," which is marked by improving patient adherence in the days around a physician office visit. This has been found in both pediatric and adult epilepsy populations, with a reported increase in adherence around the time of office visits ranging from 5% to 15%.[18,19]

Risk Factors for Antiseizure Medication Nonadherence

Frequent daily dosing is the traditional explanation for medication nonadherence. With the use of pill bottles fitted with an electronic dose counter, Cramer and colleagues[20] found that antiseizure medication adherence dropped with frequency: 87% adherence with 1 time a day, 81% with 2 times a day, 77% with 3 times a day, and 39% with 4 times a day. This study also compared other measures of nonadherence and found that neither drug levels nor pill counts correlated accurately with the electronic dose counter, finding that the first two overestimated adherence. In line with this reasoning were later studies using pill count techniques that failed to confirm frequency-adherence relationships.[21]

Antiseizure medication polytherapy may also be an important barrier to adherence.[13,21–23] Ferrari and colleagues[23] found nonadherence rates of 55% for those receiving monotherapy compared to 71% for those receiving polytherapy.

Demographics such as age and sex have no consistent effects on adherence.[13,21–23] In the authors' experience in a tertiary epilepsy clinic, the span between late adolescence and early adulthood appears to be an especially challenging time for adherence as patients begin to act independently. The few studies that have specifically examined this age group tend to agree, with adolescents or young adults demonstrating worse adherence than younger children.[8,24,25]

Socioeconomic factors play a role in antiseizure medication adherence. For example, in a study centered specifically on adherence in pediatric patients with

KEY POINTS

- **Comparatively little evidence exists for evaluating risk factors for breakthrough seizures. The available data suggest that nonadherence is the most important factor leading to breakthrough seizures.**
- **Antiseizure medication nonadherence is common and should be screened for when a patient's seizures are uncontrolled.**
- **Increasing complexity of the antiseizure medication regimen, including increased dosing frequency or increased numbers of medications, is associated with an increased risk of medication nonadherence.**

epilepsy, lower socioeconomic status was the sole factor associated with nonadherence.[17] At the other end of the age spectrum, adherence in elderly adults measured from prescription refill counts (proportion of days covered, a measurement related to medication possession ratio) in Medicare Part D found that zip codes in high poverty areas were more likely to be nonadherent than those from zip codes in wealthier areas.[26]

Race has also been shown to correlate with antiseizure medication nonadherence, with minority patients, especially those who identified as African American, at higher risk of nonadherence. In an indigent care clinic (a sample considered as a leveling factor for wealth), compared with white patients, African American patients had lower adherence equivalent to 2 days of missed antiseizure medications per month in a twice daily regimen.[27] In the population-based study by Piper and colleagues,[26] adherence was worse among African American patients (40%) compared with white patients (29%).

Lastly, psychiatric factors such as mood, anxiety, or cognition may play roles in adherence. A 2017 report from Wang and colleagues[28] suggested that moderate to severe anxiety was associated with nearly a threefold risk of nonadherence while social support may offer some degree of protection. Similarly, Ettinger and colleagues[29] found that depression was associated with medication nonadherence as well as poorer quality of life, although this was not consistent across all metrics studied.

Improving Antiseizure Medication Adherence

Methods to improve antiseizure medication adherence have not been systemically compared, but many commonly used techniques are available to the experienced physician (TABLE 3-1). Traditionally, clinicians have depended on what some could dub the "doomsayer approach," pulling out verbal tarot cards predicting, for the nonadherent, woes ranging from possible antiseizure medication adverse effects, trauma, loss of employment, loss of driving privileges, and the ultimate trump card, SUDEP. Although the last gets the attention of parents and loved ones, mortality can be an abstract concept to younger people.

Reminders may aid in adherence; those patients with smartphones enjoy a host of medication reminder–specific apps as well as a sophisticated calendar system that can be programmed for regular medication reminders. Less

TABLE 3-1 **Methods to Aid in Antiseizure Medication Adherence**

Type of Method	Intervention
Reminders	Smartphone alarm, smartphone app, pill box, premeasured pill packets
Supervision	Recruitment of family or friends, home health care, pill dispensers/ compliance auditors, school administration
Medication	Change from antiseizure medication with short half-life to one with long half-life, fill every 3 months instead of every month, alter scheduling to coincide with other cues
Programmatic intervention	Behavioral counseling, educational counseling

technical, common techniques include explicit medication lists, pill boxes, and for those patients or families who are less literate, prepackaged "blister packs" can be available that contain fixed and clearly labeled antiseizure medication doses.

Antiseizure medication supervision can aid patients who are nonadherent. Recruiting family members or friends is the most common approach, but some patients may require, depending on availability, scheduled compliance checks by home health care providers. Pediatric patients whose parents may have cognitive, social, or schedule problems can be helped by altering antiseizure medication scheduling to guarantee that at least a morning or afternoon dose is dispensed at school rather than at home.

The wily physician can sometimes aid adherence by altering antiseizure medication scheduling, eg, advising that doses can be taken with meals or with other cues rather than adhering to more "perfect" on-the-clock equal intervals. Formulations can be manipulated; patients with trouble remembering their twice daily antiseizure medication may improve with an extended release once daily formulation. Families who may have problems with monthly paychecks not extending to the end of the month or who have travel problems sometimes can benefit from antiseizure medications dispensed in 3-month rather than 1-month refills.

Finally, patients with persistent nonadherence may benefit from a more systematic approach derived from cognitive-behavioral techniques.[30] A few recent randomized controlled trials with small populations have evaluated various self-management interventions to improve adherence. Dash and colleagues[31] investigated the effect of educational intervention upon patient adherence. This study compared 90 participants in the active intervention group who received guided content including basic information about epilepsy and antiseizure medications, rationales for treatment, and techniques for coping with epilepsy, which was randomized against control participants who received standard care. Participants in the intervention arm demonstrated a statistically significant improvement in adherence questionnaire scores as well as decreased seizure frequency.

Pakpour and colleagues[32] compared 137 participants who were randomly assigned to behavioral therapy that targeted antiseizure medication adherence via counseling sessions that occurred 3 times a week that reinforced the need for adherence, explored patient concerns that may cause nonadherence, and reviewed methods to overcome these concerns against 138 control participants and found that 60% of the participants in the intervention group compared with 38% of controls had antiseizure medication levels within reference range 6 months postintervention.

Tang and colleagues[33] evaluated two types of intervention: 59 participants were randomly assigned to receive medication education alone (that included monthly calls from a pharmacist) versus 65 participants who received a combination of this educational intervention plus behavioral intervention that targeted systematic medication scheduling. Although there was no significant difference between the two groups in follow-up analysis, both groups experienced improved adherence and reduction in seizure frequency.

In summary, current data suggest that adherence may be improved by increasing patient education and providing feedback to address concerns that may be obstacles to adherence. Overall, relatively few randomized controlled

KEY POINTS

- Many demographic factors may convey an increased risk of nonadherence, including socioeconomic status and race, although other factors such as gender and age are not clearly associated with increased risk.
- Current data suggest that adherence may be improved by increasing patient education and providing feedback to address concerns that may be obstacles to adherence.

studies have evaluated methods to improve adherence in patients with epilepsy, which was recently highlighted in a systematic review by da Mota Gomes and colleagues.[30] These studies demonstrate that short-term antiseizure medication adherence can improve with active intervention.

Antiseizure Medication Monitoring

Expert guidelines suggest a limited but important role for antiseizure medication monitoring via serum concentrations.[34] Once a treatment regimen is deemed effective, a trough antiseizure medication concentration can establish a proper baseline by which to judge future problems such as toxicities or changes in effectiveness, such as breakthrough seizures or suspected nonadherence. Antiseizure medication levels can be obtained either in anticipation of or in the face of changes in health or development that may perturb steady-state levels, such as in children when they are rapidly growing, changes in clearance as the result of aging or hepatic-renal disease, or pregnancy. Drug levels may be helpful when encountering possible formulation variability or pharmacokinetic interactions when coinciding medications change.

However, regular, routine blood level monitoring of antiseizure medications is generally not needed and can even be harmful if an effective regimen is altered because the result falls outside the "normal" range. Note that nearly every indication for monitoring provided in expert guidelines depends on changes of levels within individuals, not on comparison of an individual to grouped ranges. The interpretation of normal should be done cautiously because there can be considerable variability of reference ranges across different laboratories.[35] Most importantly, what is normal for one patient may be toxic or ineffective for another. In short, serum concentrations are only part of the story; dose adjustments should not be made on the basis of levels alone but should be performed when guided by the patient's clinical state.

Antiseizure Medication Instability, Interactions, and Proconvulsants

Some patients maintain rigorous adherence but experience breakthrough seizures arising from unanticipated changes in previously stable and effective antiseizure medication regimens.

MEDICATION OR OTHER INTERACTIONS THAT MAY LOWER ANTISEIZURE MEDICATION LEVELS. Antiseizure medication levels may drop unexpectedly in a previously stable antiseizure medication regimen. Interactions between antiseizure medications, between other medications and antiseizure medications, or from dietary intake may affect antiseizure medication levels.

While a comprehensive listing of all interactions that result in the lowering of antiseizure medication levels is too extensive for this review, examples of significant interactions are discussed. Common in the authors' clinical experience is the interaction considered in the patient in CASE 3-1: the induced metabolism of lamotrigine by estrogen. Estrogen-containing compounds (as well as the menstrual elevation of estrogen in the menstrual phase of the menstrual cycle) act as inducers of the uridine 5'-diphospho-glucuronosyltransferase enzyme, which, in turn, metabolizes lamotrigine, resulting in an approximately 50% decrease in lamotrigine levels.[36,37] Progesterone, on the other hand, has little effect on lamotrigine.[32] Although interactions with enzyme-inducing antiseizure medications such as phenytoin and carbamazepine also feature

similar interactions with lamotrigine, since antiseizure medications are typically prescribed by neurologists and estrogens are typically prescribed by non-neurologists, dips in effective lamotrigine levels are more apt to arise unexpectedly because of the introduction of drugs that are not antiseizure medications.

A similar underappreciated but apparent interaction in the authors' clinical practice is between phenytoin and tobacco. Tobacco is an established inducer of multiple cytochrome P450 isoenzymes.[38] The clinical significance of this is poorly documented, but there is at least one case report of phenytoin toxicity reported with smoking cessation.[39] In the authors' experience, tobacco smoking may result in lowered phenytoin levels that persist despite attempts at increasing doses, leading to the perception of nonadherence.

Medication interactions are not limited to prescribed medications; over-the-counter medications or herbal preparations should also be routinely considered in patients with medication-responsive epilepsy. More than 50% of patients with epilepsy use herbs and dietary supplements, and 29% of those do not report these exposures to their physicians.[40] TABLE 3-2 contains a listing of commonly used herbal supplements that either decrease antiseizure medication levels or decrease seizure threshold.[41,42]

An example of an herb-drug interaction in epilepsy is ginkgo biloba, which is a known hepatic enzyme inducer and has been previously shown to decrease levels of phenytoin and valproate, which, in turn, has been documented to lead to breakthrough seizures.[41] The repercussions from such interactions can be substantial and even deadly as at least one case report exists of seizure-related death (a drowning) occurring because of the antiseizure medication–lowering effects of gingko use.[43]

PROCONVULSANTS. As noted above, many common supplements (TABLE 3-2) and prescription medications (TABLE 3-3)[44] may lower seizure threshold. In the authors' experience, the ubiquitous beta-lactam antibiotics (eg, ampicillin), which are frequently used in children who are febrile, ill, or sleep deprived, can, in the setting of epilepsy, lower seizure threshold enough to facilitate subsequent seizures. Certain psychotropic medications are also associated with an increased risk of breakthrough seizures. For example, bupropion is a commonly prescribed medication for either depression or smoking cessation. Bupropion is thought to confer a dose-dependent lowering of seizure threshold or emergence of epileptiform EEG abnormalities.[45,46] A limitation of this literature is that reports have focused on the emergence of seizures or EEG findings in the general population; studies have not focused on the specific risk to patients with epilepsy.

SWITCHING ANTIEPILEPTIC DRUGS. Breakthrough seizures may be precipitated by well-intended iatrogenesis. Changing of antiseizure medications may occur in a medically responsive patient when faced with a host of antiseizure medication–related problems. For example, the child with unexpectedly poor school performance or the adult with severe osteoporosis may require antiseizure medication switching; or an anticipated medical condition such as planned pregnancy may require replacement of teratogenic valproate with an antiseizure medication with less fetal adverse effects, and an upcoming organ transplant may require replacement of an antiseizure medication with one without interactions with immunosuppressant drugs.

KEY POINT

- Medications and supplements may cause seizures, either through interactions with antiseizure medication or through proconvulsant properties.

Switching antiseizure medications in patients with medically responsive epilepsy is not without risk. A 2016 prospective study of patients with epilepsy undergoing an antiseizure medication switch versus controls who were maintained on current therapy suggested an approximate 15% increased risk of breakthrough seizure activity over the next 6 months.[47]

Sometimes the prescribing hand of the physician is not forced by medical concerns but by patients' financial limitations. Much controversy surrounds denials by third-party payers for coverage of brand name antiseizure medications and subsequent "forced" replacement with theoretically equivalent generic antiseizure medications. The data regarding brand name to generic

TABLE 3-2

Common Medicinal Herbs, Primary Uses, and Effects on Lowering of Seizure Threshold or Antiseizure Medication Levels[a]

Herb	Typical Use	Proconvulsant Effect
Asafoetida	Memory, mood, sedative	Lowering of seizure threshold
Borage	Fever, diuretic	Lowering of seizure threshold, lowering of antiseizure medication levels
Ephedra	Cold, flu, respiratory	Lowering of seizure threshold
Ergot	Migraine	Lowering of seizure threshold
Eucalyptus	Cold, flu, respiratory	Lowering of seizure threshold
Evening primrose	Weight loss, menstrual pain	Lowering of seizure threshold, lowering of antiseizure medication effects
Ginkgo biloba	Memory, mood	Lowering of seizure threshold, lowering of antiseizure medication levels
Ginseng	Mood, erectile dysfunction	Lowering of seizure threshold
Pennyroyal	Abortion, menses induction	Lowering of seizure threshold
Sage	Hyperlipidemia, gastrointestinal symptoms	Lowering of seizure threshold
Shankhpushpi (Ayurveda)	Memory	Lowering of antiseizure medication levels
Star anise	Colic, gastrointestinal symptoms	Lowering of seizure threshold
Star fruit	Diuretic	Lowering of seizure threshold
Wormwood	Gastrointestinal symptoms	Lowering of seizure threshold
Yohimbine	Erectile dysfunction	Lowering of seizure threshold, lowering of antiseizure medication levels

[a] Data from Samuels N, et al, Epilepsia,[41] and Tyagi A, et al, Epilepsia.[42]

interchange are mixed, although the data increasingly support efficacy of generics, as recent large-scale prospective and retrospective investigations support bioequivalence between brand name antiseizure medications and generic substitutions approved by the US Food and Drug Administration (FDA), with overall no statistical difference in seizure frequency.[48,49] However, older single-site studies have suggested that brand name to generic antiseizure medication exchanges are poorly tolerated.[50] Current data also suggest that switching between different generic formulations of the same antiseizure medication is not associated with increased seizures.[51] Physicians should be vigilant about patient adherence during the initial interchange between brand and generic formulations, as evidence suggests that changes in pill appearance may increase the risk of nonadherence.[52] These data led the American Epilepsy Society to recommend routine counseling about possible changes in color and shape in generic antiseizure medication substitutions in its 2016 position statement on the topic of generic pharmacotherapy.[53]

Seizure Precipitants

Seizure precipitants are "any endogenous or exogenous factor that promotes the occurrence of epileptic seizures."[54] Seizure precipitants are different from acute symptomatic seizures in that healthy individuals will not seize when exposed to a

Drug-Drug Interactions That Depress Antiseizure Medication Levels[a] TABLE 3-3

Antiseizure Medication	Medications That Decrease Antiseizure Medication Levels
Brivaracetam	Rifampin
Clonazepam, other benzodiazepines	Rifampin, enzyme-inducing antiseizure medications
Enzyme-inducing antiseizure medications (eg, phenytoin, carbamazepine, primidone)	Enzyme-inducing antiseizure medications
Eslicarbazepine acetate, oxcarbazepine	Enzyme-inducing antiseizure medications
Felbamate	Enzyme-inducing antiseizure medications
Lamotrigine	Rifampin, estrogen, lopinavir/ritonavir, enzyme-inducing antiseizure medications
Primidone	Diuretics
Perampanel	Enzyme-inducing antiseizure medications (not primidone)
Rufinamide	Enzyme-inducing antiseizure medications
Tiagabine	Enzyme-inducing antiseizure medications
Topiramate	Phenytoin, carbamazepine
Valproate/valproic acid	Carbapenem antibiotics
Zonisamide	Enzyme-inducing antiseizure medications

[a] Modified with permission from Vossler DG, et al, Epilepsy Curr.[44] © 2018 American Epilepsy Society.

seizure precipitant, while patients with and without epilepsy may seize in the face of severe brain or systemic insults, which typify acute symptomatic seizures.[3] The reported prevalence of seizure precipitants varies widely based on practice setting. A study of a community-based practice found the prevalence of all precipitants to be 47%, while rates range higher, between 62% and 97%, at tertiary epilepsy centers[54–56] Despite a significantly wide range of estimates of the overall prevalence of seizure precipitants, data regarding specific patient-reported seizure precipitants are remarkably consistent, with stress, sleep deprivation, and fatigue being the most commonly documented (FIGURE 3-1).[54–56] Patients with different epilepsy syndromes probably have different susceptibilities among precipitants. For example, in the study by Frucht and colleagues,[54] patients with temporal lobe epilepsy cited sleep (as opposed to sleep deprivation) as a precipitant disproportionately less frequently than syndromes such as nontemporal focal epilepsy or idiopathic generalized epilepsy.

STRESS AND FATIGUE. The most commonly reported seizure precipitant is stress.[54–56] The original study of precipitant prevalence by Frucht and colleagues[54] documented that 30% of adult patients surveyed cited stress as a clear precipitant. In this study, more women (36%) than men (24%) cited stress, and the syndrome most susceptible to stress was temporal lobe epilepsy. Fatigue is a reported seizure precipitant in 13% to 15% of patients.[54–56] Isolating fatigue as a seizure precipitant is difficult, as evidence suggests that emotional stress, fatigue, and sleep deprivation are correlated with one another.[54] Stress, sleep deprivation, and fatigue are likely interrelated and may share a common pathophysiology.[54] Experimental models of epilepsy support the hypothesis that stress, especially early exposure during brain development, facilitates epileptogenic changes in stress-dependent neurotransmitters and hormone levels within the brain.[57] Observations of mass stress in humans echo animal findings; for example, seizure control worsened shortly after the terror attacks in the United States on September 11, 2001.[58]

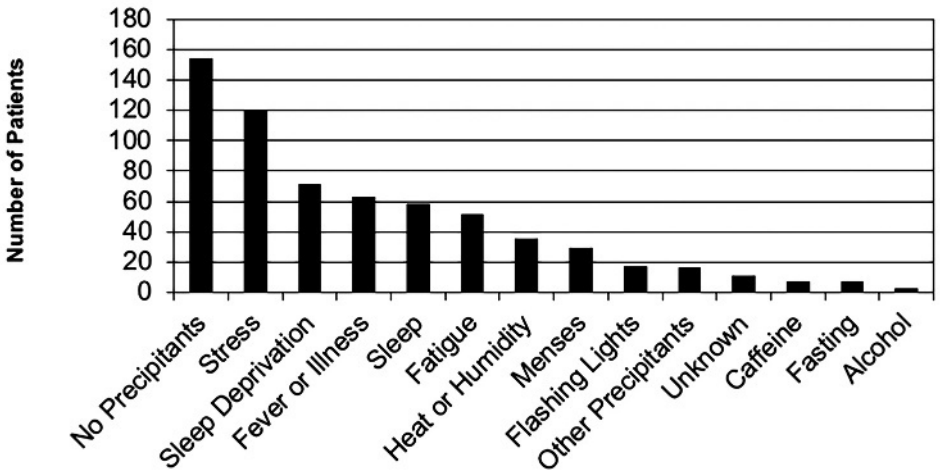

FIGURE 3-1
Distribution of seizure precipitants for 400 adult patients surveyed at a tertiary care epilepsy clinic.
Reprinted with permission from Frucht MM, et al, Epilepsia.[54] © 2000 John Wiley and Sons.

SLEEP DEPRIVATION AND INSOMNIA. Sleep deprivation is also a frequently documented seizure precipitant, estimated to occur in 18% to 25% of patients.[54,56,59] Although sleep deprivation correlates highly with stress and fatigue, sleep deprivation and insomnia require separate discussions because of the history of the use of sleep deprivation as an interictal spike– or seizure-activating procedure in routine and epilepsy-monitoring EEG.[60]

Insomnia and sleep disturbances are a common problem in patients with epilepsy, affecting 24% to 55% of patients.[61–65] Quigg and colleagues[65] documented that more than 50% of patients with epilepsy experienced some degree of insomnia, with 43% having clinically significant insomnia. Most studies correlate sleep deprivation or insomnia with worse seizure control. For example, previous diary studies[66] and surveys[8,13,54] found that patients reported that sleep deprivation provoked seizures.

Sleep deprivation and insomnia, through the enhancement of the stress response, may worsen seizure control because of dysregulation of hypothalamic pituitary function. Insufficient sleep and the "hyperarousal" of insomnia causes compensatory changes in homeostatic processes; stress hormones such as noradrenaline and corticosteroids are dysregulated in primary insomnia.[67] Altered corticosteroid responses to stress have been observed in children susceptible to stress-precipitated seizures.[68] The interactions between sleep disruptions and epilepsy may not be one way; seizures and the epileptic state may alter circadian regulation and affect sleep distribution (among other circadian rhythms).[69,70]

FLASHING LIGHTS. Flashing or flickering lights are reported as a precipitant in 4% and 17% of surveyed patients.[54,56] Flashing lights can be the cause of a reflex photosensitive epilepsy, but the discussion here will center on flashing lights as a more generic precipitant in patients with otherwise well-controlled epilepsy. Flashing lights can cause mass seizure precipitation; in 1997, television airing of a Pokémon cartoon that featured a sequence of flashing lights caused seizures in a total of 685 children, among whom were children who likely had latent epilepsy and had yet to have a seizure, and those with known epilepsy with susceptibility to photic stimulation.[71] Susceptibility to flashing lights is not distributed equally among syndromes; patients with idiopathic generalized epilepsies have 3 to 4 times the prevalence of abnormal responses to photic stimulation during EEG as those with symptomatic focal epilepsies.[72]

EXERCISE. Exercise appears to have disparate effects on groups of patients. Exercise in the form of "physical exertion" was reported by Frucht and colleagues[54] as a seizure precipitant in 9% of patients; a similar proportion also reported that becoming overheated or exposed to heat and humidity was a precipitant. Nakken and colleagues[73] similarly found 10% of patients with epilepsy reported exercise as a seizure precipitant; however, in contrast, the study also found that 36% of patients reported improvement in seizure control with regular exercise. A small randomized controlled study of exercise in epilepsy found that regular physical activity not only improved seizure frequency but also improved self-perceived "physical self-concept and vigor."[74]

ALCOHOL. Alcohol use has also been described as a seizure precipitant[54]; higher rates (15%) may be seen where alcohol use is more culturally accepted.[75] These studies did not pin down whether it was alcohol ingestion or the phase of

KEY POINTS

- Switching antiseizure medications may result in seizure recurrence, even in the setting of prolonged seizure freedom.
- Current data from large population studies suggest that generic antiepileptic drugs are bioequivalent to name brand medication.
- Stress and sleep deprivation are the most common seizure precipitants in patients with epilepsy.
- Insomnia is common in patients with epilepsy and is correlated with poor seizure control.

withdrawal that patients reported as the susceptibility. A review of alcohol use in patients with epilepsy concluded that regular use in "small amounts" (one to two drinks) neither increases seizure frequency nor affects antiseizure medication levels.[76] Greater use, however, places patients at risk of withdrawal symptoms, and lowered seizure thresholds may occur despite the absence of symptoms of frank delirium tremens, with the greatest risk of seizures occurring about 7 to 48 hours after the last drink.[77] Furthermore, the use of alcohol may combine with other precipitants such as nonadherence or sleep deprivation. Samsonsen and colleagues,[78] in a survey of patients hospitalized for seizures, found that alcohol intake was associated with decreased sleep in patients with epilepsy. Alcohol avoidance has also been reported as a self-management intervention that may improve seizure frequency.[79]

MANAGEMENT OF SEIZURES DUE TO PRECIPITANTS. Breakthrough seizures due to a precipitating factor should be considered evidence of suboptimal seizure control and predictive of more seizures.[4,7] The authors recommend the following process in evaluating breakthrough seizures. First, acute symptomatic seizures (the result of a new acute epileptogenic injury or progression in a patient with a progressive epileptic disorder) should be considered. Second, either history, detective work such as pill counts, or drug levels should establish adherence. Third, if adherent, antiseizure medication therapies should be optimized or changed, since breakthrough seizures can be considered as jumping over an inadequate seizure threshold. Fourth, the physician should attempt to identify the seizure precipitants and help strategize their avoidance. If precipitants clearly appear to be present, avoidance strategies may be sufficient without changes in the antiseizure medication regimen. Fifth, the clinician should inform the patient that adequate time be designated to consider the patient seizure free again (ie, using the rule of three to estimate how long the patient is required to be seizure free before being considered back in "safe territory").

Avoidance of endogenous precipitants such as stress and fatigue are nuanced issues. Baldin and colleagues[80] highlighted that the presence of anxiety and mood disorder were associated with stress and increased risk of breakthrough seizures. The interconnection between anxiety, depression, and stress is complex. Privitera and colleagues[81] have shown that patients with a history of depression were more likely to have stress as a precipitating factor for seizures. Evidence also suggests that stress and anxiety may be mediated by depression in patients with epilepsy.[82] These findings underpin the need for physician screening of depression and mood disorders in patients with epilepsy, not only as a means of improving mood but also to potentially optimize and maintain seizure control.

Self-management techniques have also been found to be beneficial for stress and psychiatric comorbidities associated with epilepsy.[83] In one study, mindfulness therapy, a form of meditation, was shown to decrease seizure frequency and reduce symptoms of anxiety and depression as compared to control participants, who received social support only.[33] In a small randomized controlled trial, yoga was also associated with improved quality of life and seizure frequency, although this study was limited by lack of adequate controls as both randomly assigned groups received active interventions (yoga versus behavioral therapy).[84] Cognitive-behavioral therapy for anxiety and depression has also been shown to improve mood and seizure frequency.[85,86] A recent randomized controlled trial investigated seizure and stress reduction through muscle

relaxation techniques. Patients in the treatment arm were instructed in a muscle relaxation protocol; controls were instructed in a "focused attention" protocol. Seizure frequency improved equally in both groups, but stress reduction improved significantly better in the treatment group.[87]

Deleterious effects of sleep deprivation and insomnia on seizure control can, hopefully, be helped by improvements in sleep hygiene or treatment of insomnia, although hard data are largely lacking. The following is a short list of simple sleep suggestions used in counseling patients in sleep hygiene:

- Awaken at the same time every day (eg, 6:30 AM or 7:00 AM) and do something active and in the light upon awakening
- No sleep "when the sun is up" (don't steal from nighttime sleep)
- Give yourself at least an 8-hour window for sleep, and do something "boring" before going to bed
- No caffeine past noon
- No electronics in the bedroom (eg, smartphone, computer, television)

The authors of this article provide patients these suggestions because they can be tackled by most patients and their families largely because of simplicity. Note that these sleep suggestions mediate waking behavior; patients need to be counseled that sleep cannot be forced but slips into the space prepared for it by one's daytime activities. A sleep history concentrating on time in bed, time arising, sleep fragmentation, in-bed and environmental distractions, caffeine use, and factors such as snoring and apneas can disclose sleep habits that may affect seizure control and daytime sleepiness. In the authors' experience, a sleep history is easily obtained but never given without explicit questioning. The first-line treatment for insomnia is cognitive-behavioral therapy[88]; sedative-hypnotic use should be avoided as much as possible in patients with epilepsy because of risks of polypharmacy and the fluctuation of seizure thresholds, such as in the withdrawal from and habituation to benzodiazepines. The evidence for the proconvulsant properties of medications used for their soporific effects due to activities at histamine receptors—tricyclic antidepressants, such as amitriptyline or trazodone, or antihistamines, such as diphenhydramine—is mixed.[89,90] Nevertheless, in the authors' practice, when faced with insomnia or sleep deprivation, patient education or other behavioral methods are attempted first, and sleep-aid agents with less of an epileptogenic burden such as melatonin or gabapentin are preferred.

Avoidance of flashing light exposure can be surprisingly difficult. For example, police and ambulance strobes or the stark shadows seen on bright winter days while driving through the woods can serve as unexpected sources of strong photic stimulation to drivers and passengers alike. Electronic devices feature flashing lights and rapid screen redraws, and video games still feature scenes that can provoke seizures (although guidelines for filtering especially potent light wavelengths have been legislated).[91] Special sunglasses can be tinted with colors specifically to block particularly ictogenic light spectra, although plain gray glasses may have equal effects.[92,93] Patients can be quite clever in self-treatment; one patient of the authors whose seizures were triggered by the flashing "hold" button on her office phone masked most of the light with finger nail polish, fixing the problem.

KEY POINTS

- Mood disorders are common in patients with epilepsy. Screening should be performed to address both inherent mood concerns but also to potentially improve seizure control.
- Self-management techniques may improve psychiatric comorbidities associated with epilepsy, and some evidence suggests this may translate into improved seizure frequency.
- The first-line treatment for insomnia is cognitive-behavioral therapy; sedative-hypnotic use should be avoided as much as possible in patients with epilepsy because of risks of polypharmacy and the fluctuation of seizure thresholds, such as in the withdrawal from and habituation to benzodiazepines.

CONCLUSION

Medically responsive epilepsy is more common than medically intractable epilepsy. Despite having a relatively straightforward prognosis, the longitudinal treatment of the population who are seizure free requires vigilance and education. The fundamental basics of care in this population center on a working knowledge of antiseizure medications, patient adherence, and factors that could precipitate seizures.

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