



## Review

# Dealing with the storm: An overview of seizure precipitants and spontaneous seizure worsening in drug-resistant epilepsy

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## ABSTRACT

In drug-resistant epilepsy, periods of seizure stability may alternate with abrupt worsening, with frequent seizures limiting the individual's independence and physical, social, and psychological well-being. Here, we review the literature focusing on different clinical scenarios related to seizure aggravation in people with drug-resistant epilepsy. The role of antiseizure medication (ASM) changes is examined, especially focusing on paradoxical seizure aggravation after increased treatment. The external provocative factors that unbalance the brittle equilibrium of seizure control are reviewed, distinguishing between unspecific triggering factors, specific precipitants, and 'reflex' mechanisms. The chance of intervening surgical or medical conditions, including somatic comorbidities and epilepsy surgery failure, causing increased seizures is discussed. Spontaneous exacerbation is also explored, emphasizing recent findings on subject-specific circadian and ultradian rhythms.

Awareness of external precipitants and understanding the subject-specific spontaneous epilepsy course may allow individuals to modify their lifestyles. It also allows clinicians to counsel appropriately and to institute suitable medical treatment to avoid sudden loss of seizure control.

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## 1. Introduction

The prevalence of active epilepsy is between 4 and 10 per 1000 people [1]. In most cases, adequate antiseizure treatment leads to sustained seizure freedom [2]. In about one-third of people with epilepsy, however, seizures are drug-resistant, enduring despite optimal treatment. Most people with pharmacoresistant epilepsy encounter periods of stability, with rare seizures or none at all, as well as periods with loss of seizure control. Disentangling seizure worsening due to specific provocative factors from a spontaneously fluctuating epilepsy course may be challenging. Loss of seizure control constantly hinders the ability to work or attend social events and often requires emergency treatment or hospitalization with additional health costs. We focus on different scenarios leading to seizure precipitation and discuss the possible predictable and unpredictable factors triggering seizure exacerbation in people with chronic epilepsy.

## 2. Methods

We performed a PubMed/Medline search with the following terms: 'seizure precipitants', 'seizure aggravation', 'seizure worsening', 'seizure prediction', 'epilep\* aggravation', and 'epilep\* worsening' up to February 2019. No language restrictions were applied. All items identified were assessed for relevance to the topic of the review, excluding those exclusively focused on people with new-onset seizures.

Because of the heterogeneous definition of seizure worsening in the published studies, we evaluated all those reporting an abrupt change in seizure frequency/types, independent of the underlying etiology.

In addition to the automated Medline query, we also added selected references retrieved on PubMed, Google, and Google scholar search engines as well as articles in the authors' personal files.

We categorized the available data into four main clinical scenarios: Treatment changes; External provocative factors; Intervening surgical or medical conditions; Spontaneous exacerbation.

### 2.1. Scenario 1: treatment changes

Drug-resistant epilepsy is a continuous challenge. It is essential that attending physicians enter a therapeutic alliance with the individual to

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define shared treatment goals. Seizure freedom is the main target, as a substantial improvement in quality of life is obtained only after seizures stop completely [3–5]. Individuals may, however, opt for merely reduced seizure frequency to avoid medication side effects related to treatment required for seizure freedom [5] or may wish to target particular disabling seizure types, such as convulsions.

Antiseizure treatment should thus be tailored to the wishes and needs of the individual, considering the unique clinical characteristics of that individual. Achieving the optimal balance between efficacy and tolerability often requires adjustments to the dosage of antiseizure medication (ASM). A dose reduction may trigger sudden loss of seizure control in an individual, but paradoxically, a dose increase may also occasionally lead to seizure aggravation. One of the following conditions must be fulfilled to attribute seizure aggravation to a specific ASM: an increase in seizure frequency above that previously observed, temporally associated with the culprit drug and which reverses on withdrawal or dose reduction; demonstration of a consistent effect of a given drug in a specific seizure type or syndrome identification of any other factor (e.g., Electroencephalography (EEG) features), which is predictive of drug-induced seizure deterioration; appearance of new seizure types in temporal association with a drug change [6].

Paradoxical seizure worsening may occur either as a result of a non-specific manifestation of drug intoxication or as a specific side effect in some syndromes [6]. In drug intoxication, seizure aggravation is sometimes dramatic and often accompanied by other signs of central nervous system toxicity (e.g., confusion, dizziness, brainstem and cerebellar signs). This has been reported particularly with phenytoin, which has zero-order kinetics and is prone to abrupt rises in drug levels after dosage increase, but it has also been described with other ASMs (e.g., phenobarbital, carbamazepine, tiagabine, vigabatrin, lamotrigine, gabapentin) independently from the underlying mechanism of action (reviewed in [6,7]). This is usually completely reversible after drug dosage reduction [6].

Conversely, drugs with particular mechanisms of action have been reported to induce or aggravate specific seizure types despite normal serum drug levels (Table 1). Sodium channel blockers, especially carbamazepine, may trigger absences, tonic, atonic/negative myoclonus, and myoclonic seizures [6,8–12], even in people who had previously experienced only tonic-clonic seizures [9,10]. Such effects may be particularly dramatic in children, who may develop status epilepticus [8,13,14]. Specific syndromes (e.g., absence epilepsy, juvenile myoclonic epilepsy, atypical benign Rolandic epilepsy, Landau-Kleffner, Dravet and Angelman syndromes) and EEG traits (e.g., generalized synchronous spike-and-wave activity, continuous spike-and-wave during sleep, multifocal abnormalities) are known to be particularly affected by sodium channel blocker-induced seizure precipitation [6,8,15].

Vigabatrin and gabapentin can aggravate absences in idiopathic generalized epilepsies, sometimes leading to nonconvulsive status epilepticus. Vigabatrin can also worsen tonic and myoclonic seizures while gabapentin is especially detrimental to those with myoclonic seizures [16–18].

Valproate can aggravate seizures in the setting of a drug-specific idiosyncratic hyperammonemic encephalopathy. This is characterized

by a progressive confusional state, seizure aggravation, nonepileptic myoclonus, vomiting, and focal neurological deficits, especially in people with carnitine deficiency or congenital urea cycle enzymatic defects [19].

Benzodiazepines may also precipitate seizures, which seems counterintuitive as benzodiazepines are first-line drugs in status epilepticus. Abruptly increasing tonic seizures have, however, been reported in people with Lennox–Gastaut syndrome treated by intravenous benzodiazepines; this paradoxical effect has no clear explanation, is rare, and has been reported exclusively during absence status epilepticus in individuals who had formerly experienced numerous other episodes of tonic status, sometimes provoked by other medications [20–22].

## 2.2. Scenario 2: external provocative factors

External seizure precipitants are mostly patient-reported and are highly subjective. Individuals may associate familiar and common triggers with the feeling of impending seizures rather than with seizures themselves, raising the possibility of false positives [23]. Overt seizures are the final expression of a waxing preictal phase while prodromes and auras are the initial symptoms perceived by the individual [24]. Auras are considered part of the ictal event while prodromes (e.g., behavioral changes, cognitive disturbances, anxiety, fatigue) are believed to be preictal events not associated with EEG changes, appearing from a few minutes to two days before the seizure and lasting up to several hours, with obscure physiological background [25,26]. Therefore, seizure precipitants associated with prodromes/auras are not strictly false positives since they may correspond to states of high seizure susceptibility, which may not be followed by overt seizures due to the intervention of the brain homeostatic mechanisms [23].

Most people with epilepsy report at least one seizure precipitant, with emotional stress, sleep deprivation, and tiredness as the most frequent culprits, irrespective of the underlying syndrome [27,28].

Emotional stress is reported as a seizure precipitant by over 80% of people with epilepsy [27]. This association declines with epilepsy duration but is still reported by half of those with epilepsy for over 30 years [29]. Seizures may be precipitated by acute stress [30,31], and some people report being able to foresee seizures after minor or major stressors [32], especially when experiencing preictal mood changes [33,34]. Chronic stress may also affect epilepsy control [30,35,36]. People with stress-sensitive epilepsy exhibit a distinct brain response to stress hormones. There seems to be a positive correlation between cortisol levels and interictal discharges [37] and a negative correlation between cortisol levels and global functional connectivity on EEG [38]. Anxiety and depression are especially common in people whose epilepsy is worsened by emotional stress; half of these individuals pursue stress-reduction therapies (e.g., yoga, exercise, and meditation), which appear to be beneficial in terms of seizure frequency [30,36].

Sleep deprivation is reported as a seizure precipitant by about two-thirds of people with epilepsy [27]. Sleeping for just one hour less than usual is an independent risk factor for seizure occurrence in unselected people acutely hospitalized for epileptic seizures [39]. People with generalized epilepsies, particularly juvenile myoclonic epilepsy, are especially prone to this [40–44]. Sleep deprivation seems less important in people with drug-resistant epilepsy who suffer daytime sleepiness and are therefore less likely to be exposed to sleep deprivation [45].

More than half of people with drug-resistant epilepsy report fatigue as a seizure precipitant [27], either as a nonspecific preceding condition or as specific premonitory symptoms corresponding to a prodromal high-risk seizure state [33,46–48].

Alcohol intake as either chronic abuse or binge drinking is another common provoking factor. Intoxication by alcohol may trigger seizures because of a direct neurotoxic effect, or to the increased risk of head trauma and medical complications. Antiseizure medication levels can also be substantially lowered in chronic users [49]. Excessive acute alcohol intake acts as a direct proconvulsant agent with a dose-dependent

**Table 1**  
Seizure worsening induced by antiseizure medication.

Seizure type	Worsened or de novo induced by
Typical and atypical absences	CBZ, GBP, LCM, LTG, OXC, PGB, PHT, TGB, VGB
Myoclonic	CBZ, GBP, LTG, OXC, PGB, PHT, TGB, VGB
Negative myoclonus and atonic seizures	CBZ, LTG
Tonic seizures	BDZ, CBZ, OXC

BDZ, benzodiazepines; CBZ, carbamazepine; GBP, gabapentin; LCM, lacosamide; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; TGB, tiagabine; VGB, vigabatrin.

effect while the effect of alcohol withdrawal on seizure occurrence is less clear and possibly confounded by the detrimental effect of chronic alcohol exposure [50]. Social drinking is rarely associated with seizure precipitation in focal epilepsy but may affect seizure control in generalized syndromes, especially when associated with sleep deprivation [51]. People with epilepsy should therefore be counseled to use alcohol in only moderate amounts (less than two units/day). Those with higher intake should be warned of an increased risk of seizures, especially from 7 to 48 h after the last drink [49,52].

Illicit drug abuse may also negatively affect seizure control [27]. Cocaine, heroine and opiates, amphetamines and substituted amphetamines including Methylenedioxymethamphetamine (MDMA), are known to cause seizures in the general population and to exacerbate seizures in people with epilepsy [53–55]. The effect of cannabis abuse is less clear as there are reports of seizure worsening [56] and of improvements [57,58]. Overall, most do not report a substantial effect on seizures [49]. A particularly detrimental effect has been reported anecdotally in people with juvenile myoclonic epilepsy [49]. Such observations may be biased by the concomitant occurrence of sleep deprivation and missing medication in a syndrome that is sensitive to these two factors [49]. A distinction should be made between recreational cannabis use and the possible therapeutic advantages of selected compounds in epilepsy treatment [59]. Studies (reviewed in [59,60]) have demonstrated an anticonvulsant effect of cannabidiol (CBD), the main nonpsychoactive cannabis compound, leading the Food and Drug Administration to license its therapeutic use in Dravet and Lennox–Gastaut syndromes [61]. Conversely, the main psychoactive compound (tetrahydrocannabinol (THC)) has mixed effects on the seizure threshold and is associated with detrimental cognitive and behavioral effects [62–65].

Seizure exacerbation may also result from exposure to very specific provocative stimuli with a ‘reflex’ mechanism. Such ‘reflex seizures’ are consistently and objectively induced by identifiable and specific triggers [66–68].

Seizures induced by photic stimulation are the most common ‘reflex seizures’ and occur mainly in idiopathic generalized epilepsies, but also in progressive myoclonic epilepsies, in epileptic encephalopathies and, more rarely, in temporal lobe epilepsy [69–72]. People with photosensitive seizures exhibit a characteristic EEG trait, the photoparoxysmal response. This is a highly heritable endophenotype that may also occur in healthy subjects, especially in relatives of people with photosensitive epilepsies [73–76].

The EEG photic stimulation clinical protocol is performed with stroboscopic intermittent stimuli at 1–60 Hz [77]. Studies performed after major seizure incidents in children and adults watching television and playing videogames [78–81] found low luminance deep-red flickers to be more provocative than conventional black-and-white stroboscopic stimulation, activating complex cortical and subcortical networks [82, 83]. Specific broadcasting guidelines have been developed to limit the exposure to such activating stimuli, greatly enhancing the safety of people with epilepsy watching television and playing videogames. The introduction of Liquid Cristal Display monitors, rather than cathode ray tubes, may also have helped [84,85]. Nevertheless, potentially provocative stimuli may still be encountered in everyday life. In people with photosensitive epilepsies, preventive strategies include avoiding flashing lights, occluding one eye in front of provocative stimuli (e.g., stepping outdoors on a sunny day, objects with luminance variance), watching television from a distance of at least 2 m in a well-illuminated room, and using color filtering or specific lenses [81,86,87].

More rarely, reflex seizures result from music, eating, swallowing, somatic sensory or proprioceptive stimuli, reading, or hot water. In all these cases, preventive strategies consist of avoiding the specific stimulus, whenever possible [68].

Seizures induced by fever are not classed as reflex seizures, but there are specific epilepsy syndromes in which elevation of body temperature consistently precipitates seizures. Body heating whether caused by

fever, warm water, ambient warmth, or physical exercise is a very specific and powerful seizure trigger in Dravet syndrome. This is caused by loss-of-function mutations affecting the temperature-sensitive SCN1A sodium channel [88]. Fever-sensitivity is also common in milder phenotypes associated with SCN1A mutations, such as generalized epilepsy with febrile seizures plus [89] and in girls with protocadherin 19 (PCDH19) mutations [90].

### 2.3. Scenario 3: intervening surgical or medical conditions

In neurosurgical practice, seizures are not rare. Individuals who have surgery for acquired brain lesions (e.g., brain tumors, vascular malformations, traumatic brain injuries) may experience seizures similar to those who undergo surgical treatment for drug-resistant epilepsy (i.e., epilepsy surgery). People with brain tumors are especially prone to preoperative symptomatic seizures; drug-resistance is common in cortical-located tumors with low growth potential, defined as long-term epilepsy associated tumors (LEATs; e.g., dysembryoplastic neuroepithelial tumor (DNET), gangliogliomas) [91–93] [94]. After surgery, 60–90% of people with brain tumors become seizure-free; this is particularly associated with LEATs, gross total resections, earlier surgical therapy, improved overall functional status, and lack of preoperative generalized seizures [92,95]. Nevertheless, seizures may also arise as a surgical complication. ‘Early seizures’ occur in the first week after craniotomy in up to one-third of cases. This is irrespective of the occurrence of preoperative seizures and of the underlying neuropathology, due to an immediate posttraumatic effect (cerebral edema, local inflammation, excitotoxic damage, oxidative stress, impairment of neuron metabolism). This may also sometimes lead to convulsive or nonconvulsive status epilepticus [96–98]. The course of epilepsy can also be affected for the worse in individuals with tumor recurrence or incomplete resection [93,95,99].

Epilepsy surgery aims to control medical-resistant epilepsy by resecting or disconnecting the epileptogenic zone [100–102]. The epileptogenic zone is defined during presurgical workup by merging clinical, neurophysiological, and neuroimaging data in people with an overt epileptogenic lesion (e.g., hippocampal sclerosis, malformations of cortical development) and in those with normal brain imaging [102].

Early preoperative seizures may complicate the outcome [103], but the prognosis of epilepsy surgery is largely favorable in the long term with 70% of people experiencing greater than 50% seizure reduction at 10 years [104]. Nevertheless, postoperative epilepsy worsening in terms of increased seizure frequency may occur in up to 10% of cases. Rarely, individuals can develop seizure types they had not had previously, such as convulsions or status epilepticus [105]. Risk factors for seizure worsening following epilepsy surgery include extratemporal resections, incomplete resections, variable seizure semiologies, and multiple recorded ictal patterns [105–107]. These individuals should be carefully followed up, may require drug adjustments, and may be offered surgical reintervention after a comprehensive reassessment [108].

Comorbid medical conditions may also affect seizure control. About half of people with active epilepsy suffer at least one comorbid disease [109], some of which have a negative influence on epilepsy prognosis [110,111]. Migraine is associated with a reduced probability of seizure freedom [112] and psychiatric disorders to a higher risk of pharmacoresistance [113] and to an unfavorable outcome after anterior temporal lobectomy [114]. Type 1 diabetes affects about 1% of people with drug-resistant epilepsy [115]. A shared genetic/autoimmune background has been postulated [115–119]. In those with epilepsy – diabetes comorbidity, acute seizures provoked by hyperglycemia, and hypoglycemia may occur, complicating the interpretation of the epilepsy course and drug management. Chronic glycemia fluctuations may also induce neuronal damage [120–123], possibly facilitating seizures in the long term.

We may also expect seizures to be precipitated by the same factors that cause abrupt seizures/status epilepticus in the general population, including acute metabolic disorders, stroke, and infectious disorders [124].

Women with epilepsy may be especially exposed to fluctuations in seizure control during pregnancy and the menopause. Ideally, in those with drug-resistant epilepsy, conception should be planned in order to minimize the exposure to ASMs during the first trimester. Drug management is particularly delicate, as a planned reduction of dosage/number of ASMs is sought to lower the risk of congenital malformation, but this increases the likelihood of seizure worsening in the first trimester [125–127]. Early seizure deterioration may especially occur after withdrawal of valproate, which is burdened by the highest teratogenic potential [127,128]. Seizures may also worsen from the first to second or third trimesters (about 15% of all pregnancies), requiring a reinforcement of the ASM regimen [126,129]. Women taking lamotrigine may be especially prone to seizure aggravation [126,129] because the drug levels of this ASM decrease steeply over pregnancy, requiring careful monitoring and drug adjustments [130].

Menopause may also affect epilepsy, but the effect on seizure control is largely unpredictable. About 40% of women with chronic epilepsy report postmenopausal seizure worsening, and 27% describe seizure improvement [131]. A direct effect of hormonal variations is likely as women with catamenial epilepsy tend to improve both during pregnancy [132] and after the menopause [133]. Intake of hormonal replacement therapy, however, negatively affects seizure control [134].

Therapeutic drugs taken for several medical conditions may also precipitate seizures in people with epilepsy. A systematic review classified therapeutic agents according to their intrinsic epileptogenic potential: meperidine, sevoflurane, clozapine, and cyclosporine (high); propofol, maprotiline, tricyclic antidepressants, and chlorambucil (intermediate); fluoroquinolones, carbapenems, bupropion, and iodinated contrast media (low) [135]. Several other drugs have been reported as having a negative effect on seizures, either directly or by inducing the metabolism of ASMs. For example, ephedra dietary supplements have been associated with seizures because of the direct toxic effect of ephedrine [136] while exogenous estrogens administered for assisted reproduction might lead to seizure precipitation by lowering the seizure threshold and inducing glucuronidation in women taking lamotrigine [137].

#### 2.4. Scenario 4: spontaneous exacerbation

People with epilepsy may experience sudden spontaneous deterioration in seizure control. This is a difficult clinical scenario, as usually neither the clinician nor the individual concerned foresees the abrupt change in seizure frequency, which may require emergency treatment.

The periodic exacerbation of seizures was reported in the first descriptions of epilepsy in 2000 B.C. in Mesopotamia, and interpreted in relation to moon cycles. In pre-Hippocratic Ancient Greece, the ‘sacred disease’ was considered to wax and wane and be influenced by Selene, the Moon goddess [138]. Until the Middle Ages, the term

‘lunaticism’ referred to epilepsy [139,140] (Table 2). The scientific approach has disentangled epilepsy from superstitious beliefs, while still acknowledging the existence of cyclical loss of epilepsy control [141,142]. More recent studies focusing on the long-term prognosis of epilepsy showed that up to one-third of people with drug-resistant epilepsy show a relapsing–remitting course [2,106,107,143–148].

Prompted by such observations, several groups have attempted to develop machine learning algorithms based on various combinations of EEG, electrocardiogram (ECG), accelerometry, movement, and audio and video parameters to predict seizure occurrence, with inconclusive results (reviewed in [149]).

Recently, the relationship between EEG discharges and seizure occurrence at population and individual level has been investigated. Each individual with epilepsy seems to display a highly specific endogenous circadian rhythm of seizures and interictal spikes. About one-third also exhibit subject-specific ultradian rhythmicity, with periodic breakthrough of seizure clusters [135]. Seizures are facilitated by the sleep–wake transition, but the effect of sleep on spike and seizure generation cannot completely explain circadian cyclicity as individuals may develop seizures at fixed hours, even though fully alert [150]. Clock (Circadian Locomotor Output Cycles Kaput) genes (e.g., *CLOCK* and *BMAL1*) and circadian transcription factors (e.g., *CLOCK*–*BMAL1*) are likely to play a role, influencing cortical excitability and seizure threshold [151–154].

Monthly cyclicity may be partly related to the menstrual cycles in females [155], but males can also have monthly periodicity [156–158], and both may have nonmonthly ultradian cycles, over multiple days, weeks, or months [154,159].

The consistency of cortical-recorded spikes and seizure rhythmicity has been demonstrated long term (up to 10 years) with a complex clinical/neurophysiological relationship. Interictal discharges may increase, decrease, or remain unchanged before a single seizure [150,160], yet seizures preferentially occur during the rising phase of a multiday spike cycle [160].

The knowledge of individual-specific circadian and ultradian cycles may help to foresee seizure occurrence. Implantation of long-term EEG monitoring devices has recently been suggested to gauge and forecast seizure risk, but technical challenges remain [161].

### 3. Conclusions

People with drug-resistant epilepsy have frequent challenges with seizures, whose onset and course are often unpredictable. Days of recurrent seizures may be extremely discouraging, greatly limiting self-confidence and independence. Identification of precipitating events allows individuals to anticipate abrupt worsening and to modify their lifestyles accordingly. From the clinician’s viewpoint, comprehensive knowledge of the endogenous and exogenous provocative factors may allow appropriate counseling of the individual and institution of appropriate medical treatment. A deepened understanding of the cyclical course of epilepsy in each individual would allow further tailored care and prediction.

**Table 2**  
Timeline of historical descriptions on the fluctuating course of epilepsy.

Historical period	Description
2000 BC, Mesopotamia	Ancient Akkadian texts describe epilepsy as ‘antasubbū’ (the hand of sin) brought about by the god of the moon [162].
718–612 BC, Babylonia	Babylonians distinguish epilepsy with diurnal and nocturnal seizure clusters [163].
Pre-Hippocratic Greece	People who offend Selene, the goddess of the moon, are afflicted by periodic seizures [138].
400 BC, Hippocrates	Precipitating factors of seizures: changes of the winds and temperature, exposure of the head to the sun, crying, and fear [138].
Medieval times	Epilepsy as a vengeance of the goddess of the moon. The waxing moon supposedly heated the atmosphere surrounding the earth, which in turn melted the human brain and provoked the attack [164,165].
Eighteenth century (1739)	Sir Hans Sloane wrote on the relationship between moon cycles and seizure occurrence [166].
Nineteenth century (1857)	First description of catamenial epilepsy by Sir Charles Locock at the Queen Victoria Hospital, London [167].

## Declaration of Competing Interest

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