REUE | Consensus Statement

Recommendations for prescribing pharmacologic prevention during Emergency Department treatment of epileptic seizures

Recomendaciones en el tratamiento farmacológico preventivo de crisis epilépticas en urgencias

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Introduction

Spanish emergency departments (EDs) perform over 30 million consultations per year. In times of crisis, pandemics, and the growing demand for immediacy, they play a central role in the Spanish National Health System (SNS), operating 24/7/365.[1] Epileptic seizures (ES) account for up to 1% of all emergency visits.[2]

The phrase "time is brain" applies to epileptic seizures too, emphasizing the need for prompt action.[3] A joint document developed by the Spanish Society of Epilepsy (SEEP), the Spanish Society of Neurology (SEN), and the Spanish Society of Emergency Medicine (SEMES) defined the concept of urgent epileptic seizure (UES), established consensus on acute-phase treatment, and proposed a "Seizure Code".[4] It has been identified that status epilepticus (SE) represents 10% of all ES attended in EDs, with variations depending on the SE subtype.[5-9] Another 20% typically consist of cluster seizures (CS),[7,9] while the remaining cases are isolated ESs, with or without risk factors for UES.

In immediate management, an "early dual therapy" approach has been proposed for patients with UES — including SE, CS, and high-risk isolated seizures.[7,9] However, the need or appropriateness of an "early preventive pharmacologic treatment" following recovered ES without risk factors remains unclear. Many anti-seizure drugs (ASD) lack a clearly demonstrated antiepileptic effect.[10]

In an initial study from the ACE-SUR registry, it was observed that 1 in 3 adult patients treated at the ED exhibited an index seizure, and in 40% of these cases, preventive treatment was initiated. Two-thirds of patients had a known epilepsy diagnosis, and 33% of these were started on a new ASD.[7] It was also noted that prescription of a new preventive ASD at discharge occurred in 54% of patients older than 75 years vs 42% in younger individuals.[11] Among patients discharged from ED after an index seizure, clinical decision-making was considered appropriate in 85% of cases, with initiation of an ASD in 58% and no initiation in the remaining 42%. Proper preventive treatment in ED demonstrated a protective effect, reducing adverse outcomes (especially seizure recurrence and ED revisits) from 52% down to 22%.[12] Therefore, delaying preventive treatment decisions, particularly after a first ES, does not appear to be the best option.

Based on the above, we deemed it necessary to prepare a guideline manuscript to assist physicians attending patients with ES in ED in decision-making regarding preventive treatment with ASDs.

Methodology

For this document, members of the Neurological Emergencies Working Group of SEMES (NEURO-SEMES), responsible for the epilepsy area, reviewed the preventive pharmacologic treatment of adult patients with first-time ES and those with decompensated epilepsy in ED. A draft was prepared and discussed in an initial meeting among the authors and later in another session with the rest of the working group. The final manuscript was then reviewed by 4 expert epileptologists from the SEEP and the SEEN, who had previously collaborated on a consensus document with SEMES, serving as external reviewers.

Anti-Seizure drugs (ASD) in emergency care

Understanding the effect of ASDs requires some knowledge of their mechanism of action, which remains an area of ongoing research. Epilepsy involves an increase in neuronal excitability, due to enhanced excitatory and reduced inhibitory mechanisms. The onset of a paroxysmal discharge depends on the activation of voltage-gated sodium channels and glutamatergic receptors such as

Table 1. Anti-Seizure drugs (ASD): main characteristics

Active ingredient	Mechanism of action	Pharmacological profile	Indications
Phenytoin (PHT)	Inactivation of sodium channels	Nonlinear kinetics, strong enzyme inducer, high protein binding (PB), hepatic metabolism.	Focal seizures with or without secondary generalization (not myoclonic or absence).
Carbamazepine (CBZ)			
Oxcarbazepine (OXC)		Nonlinear kinetics, medium PB, crosses the BBB, hepatic > renal metabolism.	
Eslicarbazepine (ESL)			
Lamotrigine (LTG)		Nonlinear kinetics, medium PB, hepatic > renal metabolism.	Focal and generalized seizures (including absence). Lennox–Gastaut syndrome.
Lacosamide (LCS)	Slow inactivation of sodium channels	Linear kinetics, low PB, renal > hepatic metabolism.	Focal seizures with or without generalization.
Zonisamide (ZNS)	Inactivation of sodium and calcium channels	Nonlinear kinetics, moderate PB, hepatic > renal metabolism.	
Levetiracetam (LEV)	SV2A modulation; blocks calcium channels	Linear kinetics, low PB, hepatic > renal metabolism.	Focal and generalized seizures (myoclonic or tonic–clonic).
Brivaracetam (BRV)			Focal seizures with or without generalization.
Valproic acid (VPA)	GABAergic agonist; inhibits glutamate	Nonlinear kinetics, strong enzyme inducer, high PB, hepatic metabolism.	Generalized seizures (including absence). Avoid in young women.
Topiramate (TPR)		Nonlinear kinetics, weak enzyme inducer, hepatic metabolism.	Focal and generalized seizures (including absence). Lennox–Gastaut syndrome.
Perampanel (PER)	Inhibits glutamate (AMPA receptor blocker)	Nonlinear kinetics, high PB, weak inducer, hepatic metabolism.	Focal seizures with or without generalization (monotherapy pending approval).

PB: protein binding; BBB: blood–brain barrier; metabolism: hepatic (liver), renal (kidney).

NMDA (N-methyl-D-aspartate). The discharge is synchronized and sustained through voltage-gated calcium channels and glutamatergic receptors (NMDA or AMPA [α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid]), among others. SV2A proteins participate in calcium-mediated neurotransmitter release. The propagation and amplification of this discharge depend on the inactivation of inhibitory mechanisms, such as voltage-gated potassium channels and GABAergic receptors.[10]

Since the introduction of barbiturates over a century ago, the number of ASDs has steadily grown. The "classic" or first-generation drugs include phenytoin (PHT), carbamazepine (CBZ), and valproic acid (VPA). Second-generation agents include lamotrigine (LTG), topiramate (TPR), oxcarbazepine (OXC), zonisamide (ZNS), and levetiracetam (LEV). The most recent, third-generation ASDs include eslicarbazepine acetate (ESL), lacosamide (LCS), perampanel (PER), brivaracetam (BRV), and cenobamate (CNB).[13]

Benzodiazepines (BZD), which exert a GABAergic effect, are key ASDs used in first-line acute-phase treatment. There is sufficient evidence to recommend early administration of a BZD, not only in seizures lasting longer than 1–2 minutes, but also after resolved tonic–clonic seizures or cluster seizures.[1,4] Their efficacy decreases over time following the seizure,[14] so they are not usually prescribed as preventive agents in emergency care and are therefore excluded from this manuscript.

When selecting an ASD, clinicians must consider the type of seizure (generalized or focal), patient profile (comorbidities, polypharmacy, adherence), and drug characteristics, remembering that the ideal drug should have a broad spectrum, linear kinetics, no significant interactions, and minimal severe adverse effects, achieving a good efficacy-safety balance. At the ED setting, parenteral availability is also essential.[2,15-17]. Tables 1, 2, 3 summarize the main mechanisms of action, pharmacological characteristics, adverse reactions, and dosage and administration routes.

At present, there is insufficient evidence to identify a single ideal ASD.[18]

– LEV is the most widely used ASD at the ED setting.[7] It is safe, with efficacy comparable to classic ASDs such as PHT and VPA,[19] and has a broad spectrum covering focal, generalized tonic–clonic, and myoclonic seizures.[20] After years of use, psychiatric adverse effects have been reported, which may limit its use in certain patients.[21] It is considered the ASD of choice in prehospital settings.[4]

– BRV, an evolution of LEV, has fewer psychiatric side effects and demonstrates faster onset and higher potency, both as adjunctive therapy and in monotherapy, although the latter is still pending approval in Spain.[22,23]

– LCS is the 2nd most prescribed ASD at the ED sting[7] and has been proposed as a first-line option in this setting.[4] It is effective in SE and exhibits a favorable pharmacological profile.[24,25]

– VPA remains the treatment of choice in idiopathic generalized epilepsy, except in women of childbearing age and patients with hepatic impairment.[26,27] As alternatives, ESL and other carbamazepine derivatives (CBZ, OXC) are recommended for focal seizures,[26-28] while PHT has fallen into disuse[7] and is not recommended due to its poor safety profile.[4]

Recent expert consensus recommends LEV or VPA for monotherapy initiation in generalized seizures,[29] and LCS or ESL for focal seizures,[30] with LTG as an alternative.[29,30] ZNS is another broad-spectrum option,[26] and PER, with its novel mechanism of action, is also gaining recognition, even as monotherapy.[31]

Despite the availability of new ASDs, epilepsy remains pharmacoresistant in up to 40% of patients.[32] Two or more ASDs are frequently prescribed[7] as part of a rational polytherapy.[33] Ideally, ASDs with a multimodal action should be combined, achieving a good balance between efficacy and safety. The combination of ASDs with the same mechanism of action is generally avoided; instead, a sodium channel–

Table 2. Anti-Seizure drugs (ASD): precautions and adverse effects

Active ingredient	Precaution/Contraindication	Adverse effects	
		Dose-dependent	Idiosyncratic
Phenytoin (PHT)	Heart disease, lung disease, liver disease, HIV, OC, mental illness	Confusion, dysarthria, ataxia, diplopia	Agranulocytosis, anemia, liver disease, lupus, hirsutism, pseudolymphoma, neuropathy, Stevens–Johnson syndrome
Carbamazepine (CBZ) Oxcarbazepine (OXC) Eslicarbazepine (ESL)	Heart disease, lung disease, kidney disease (dose adjustment), liver disease, HIV, OC	Drowsiness, headache, diplopia, hyponatremia	Agranulocytosis, aplasia, liver disease, lupus, pancreatitis, dermatitis, Stevens–Johnson syndrome
Lamotrigine (LTG)	Liver disease, HIV	Dizziness, tremor, nausea, diplopia, skin rash	Stevens–Johnson syndrome / TEN, aseptic meningitis
Lacosamide (LCS)	Atrioventricular (AV) block	Dizziness, nausea, diplopia	PR prolongation, neutropenia
Zonisamide (ZNS)	Kidney disease (dose adjustment)	Ataxia, confusion, nausea, depression, anorexia	Stevens–Johnson syndrome, anemia, agranulocytosis, nephrolithiasis
Levetiracetam (LEV)	Kidney disease (dose adjustment), mental illness	Irritability, depression	Angioedema, psychosis, Stevens–Johnson syndrome
Brivaracetam (BRV)	Kidney disease (dose adjustment)	Drowsiness, irritability	Bronchospasm, leukopenia
Valproic acid (VPA)	Liver disease, HIV, OC, women of childbearing potential	Tremor, dizziness, weight gain, alopecia, bruising	Agranulocytosis, anemia, hepatotoxicity, Stevens–Johnson syndrome, polycystic ovary syndrome
Topiramate (TPR)	Kidney disease (dose adjustment), mental illness	Depression, paresthesias, aphasia, weight loss	Myopia, glaucoma, nephrolithiasis, oligohidrosis, hyperthermia
Perampanel (PER)	Mental illness, elderly patients	Irritability, depression, falls, weight gain	Severe neuropsychiatric effects (aggression)

blocking ASD is usually paired with another that acts through a different mechanism. Documented synergistic effects have been observed between VPA + LTG and, more recently, between LEV + LCS.[34] Initial monotherapy with one of the latter 2 after a first epileptic seizure, or their combination in patients with epilepsy, is probably one of the most advisable options in EDs today.

Preventive treatment after an index epileptic seizure in the emergency department

Diagnosis of ES

Before considering the need to initiate preventive treatment, it is essential to establish an accurate diagnosis of the ES, which is primarily clinical.

ESs are defined as a transient occurrence of signs and/or symptoms resulting from sudden, rapid, synchronous, and excessive discharges of brain cells, which, when recurrent, cause similar or stereotyped signs. ESs can be focal (formerly called partial in the previous ILAE classification), with or without predominant motor symptoms, and with or without altered consciousness (previously called complex). Generalized seizures involve both hemispheres, with predominant motor symptoms and altered consciousness in tonic–clonic seizures, preserved consciousness in myoclonic seizures, and no motor symptoms in absence seizures. The latest ILAE classification also includes ES of unknown or unclassifiable origin.[35] Most critical phenomena in ESs are positive, and negative signs are exceptional. A postictal phenomenon lasting < 30 minutes is highly sensitive and serves as a key differentiating feature from non-epileptic seizures. However, without an electroencephalogram (EEG), it is often difficult to distinguish them. Lateral tongue biting is a more specific but infrequent sign.

As in many other emergency situations, semiology is crucial for the diagnosis and even localization of the lesion.[36]

– Frontal lobe seizures are usually focal with altered consciousness and/or tonic–clonic evolution (formerly called secondarily generalized). Prominent motor features include head version, contralateral paresis, or hypermotor behavior. Complex automatisms involving salivation, chewing, swallowing, or language disturbances (such as dysarthria, aphasia, gesticulation, or vocalizations) may also occur.

– Temporal lobe seizures are generally focal non-motor and may present as somatosensory auras, such as unpleasant smells or tastes, or as vertigo, autonomic, visual, or psychic phenomena, which are often difficult to recognize. Oral or manual automatisms, staring, pupil dilation, or mutism may also be observed.

– Parietal lobe seizures are more difficult to distinguish because they manifest with subjective symptoms, often somatosensory in nature.

– Occipital lobe seizures are typically focal, presenting with visual auras such as flashes, contralateral visual field phenomena, or complex visual hallucinations. They frequently propagate, leading to secondary semiology from the affected cortical region.

When tonic–clonic seizures persist for > 5 minutes, or other types for 10–15 minutes, this is defined as SE; it is refractory if it does not resolve after two ASDs at appropriate doses. When seizures are self-limited but recur within 24 hours, they are classified as cluster seizures CS.[9,37] The ADAN scale (Aphasia or language disturbance, Deviation of gaze, Automatism, and Number of seizures) provides a simple way to identify patients with ES at risk of developing SE.[38] In cases of repeated unprovoked seizures, or even after and index seizure in the presence of a predisposing structural abnormality, a diagnosis of epilepsy may be established.

Differential diagnosis should include clinical entities that can mimic ES. Special attention should be paid to

Table 3. Anti-Seizure drugs (ASD): administration schedule

Active ingredient	Initial dose	Maintenance dose	Maximum dose
Phenytoin (PHT)	100 mg every 8 h PO 15–18 mg/kg/24 h IV	100 mg every 8 h PO 5–7 mg/kg/24 h IV in 3 doses, 24 h after loading	200 mg every 8 h PO
Carbamazepine (CBZ)	200 mg every 12–24 h PO	200 mg every 8 h PO (increase by 100 mg/day per week)	400 mg every 8 h PO
Oxcarbazepine (OXC)	300 mg every 12–24 h PO	300 mg every 12 h PO (increase by 300 mg/day per week)	600 mg every 12 h PO
Lamotrigine (LTG)	50 mg/24 h PO	100–200 mg/day in two doses (increase by 50 mg/day per week)	250–500 mg/24 h PO
Eslicarbazepine (ESL)	400 mg/24 h PO	800 mg/24 h PO (increase by 400 mg/day per week)	800–1,200 mg/24 h PO
Lacosamide (LCS)	50 mg every 12 h PO 100–200 mg IV*	100–200 mg every 12 h PO (increase by 100 mg/day per week)	300 mg every 12 h PO 250 mg/24 h in RI
Zonisamide (ZNS)	100 mg/24 h PO (weeks 1–2)	200 mg/24 h PO (weeks 3–4)	300 mg/24 h PO (weeks 5–6)
Levetiracetam (LEV)	250–500 mg every 12 h PO 500–1,000 mg IV*	500–1,000 mg every 12 h PO (increase by 250–500 mg/day per week)	1,500 mg every 12 h PO 250–1,000 mg every 12 h in RI
Brivaracetam (BRV)	25–50 mg every 12 h PO 50–100 mg IV*	50–100 mg every 12 h PO (increase by 25–50 mg/day per week)	100 mg every 12 h PO
Valproic acid (VPA)	10–20 mg/24 h PO 10–15 mg/kg IV over 5 min	200–500 mg every 8 h PO 1 mg/kg/h after 30 min IV	2,400 mg/24 h PO 25 mg/kg IV
Topiramate (TPR)	25 mg/24 h PO	50–100 mg/24 h PO (divided in 2 doses) 25–50 mg/24 h for 1–2 weeks	100–200 mg/24 h PO
Perampanel (PER)	2 mg/24 h PO	4–8 mg/24 h PO	12 mg/24 h PO

PO: oral route; IV: intravenous route; *PO: IV conversion ratio 1:1; RI: renal impairment.

convulsive syncope, for which the Sheldon algorithm is a simple and useful tool for accurate identification.[39] Other conditions include stroke, migraine attacks, transient global amnesia, and psychogenic nonepileptic seizures (PNES), which are characterized by non-congruent or functional symptoms, such as eye-opening resistance or pelvic thrusting.[40]

Currently, there are no diagnostic biomarkers for ES. Hyperlactatemia is common in convulsive episodes, and electrolyte disturbances (calcium, magnesium, phosphorus) are nonspecific. Neurogranin is a promising biomarker, though evidence remains limited.[41] Other markers, such as S100B or enolase, have shown some diagnostic value in SE.[42]

Regarding supplementary tests, in the case of an index ES, it is recommended to perform blood tests, an electrocardiogram, and microbiological and radiological studies aimed at identifying possible underlying causes. An urgent baseline cranial computed tomography (CT) scan is indicated after a first ES and in recurrent seizures if they are associated with head trauma. It may be avoided when there is a clear current toxic-metabolic origin or when recent neuroimaging provides a definitive explanation. A multimodal CT, currently available within stroke protocols, includes perfusion CT, which in patients without lesions compatible with stroke has made it possible to identify areas of increased flow or delay, thus aiding in the urgent diagnosis of ES.[43] Lumbar puncture is recommended when seizures are suspected to be due to infections of the central nervous system (CNS) or subarachnoid hemorrhage, provided that fundoscopy is normal or the CT is inconclusive. Finally, all patients presenting with urgent ES, especially those with a first seizure or with suspected non-convulsive status epilepticus (NCSE), should undergo an EEG as early as possible—ideally upon arrival or at least before discharge from the ED.[44] There is growing evidence and understanding of the diagnostic and therapeutic value of EEG in the ED[45] and in intensive care units (ICUs),[46] within expert-guided telemedicine[47] programs or using screening devices such as CERIBELL.[48]

In summary, the goal is to reach a diagnosis of acute symptomatic seizure caused by a structural lesion or toxic-metabolic disorder, or a remote symptomatic unprovoked seizure of structural or unknown etiology. This approach allows for the optimal initiation of ASD treatment in the ED setting.

Preventive treatment

When discussing treatment after an index ES, we are referring to secondary prevention, as primary prevention is not indicated, except in certain situations such as craniotomy or severe traumatic brain injury (Glasgow Coma Scale < 8).[2,12] In patients with intracranial hemorrhage, there is no consensus; however, European guidelines do not recommend prophylactic treatment.[49]

Secondary prevention aims to reduce ES recurrence,[2,12,50] prevent emergency revisits or hospitalizations, and minimize complications such as associated morbidity and mortality; falls and fractures; metabolic acidosis and rhabdomyolysis; hepatic and renal failure; stress-induced cardiomyopathy (Takotsubo syndrome); neuronal damage (eg, hippocampal atrophy, short-term memory impairment); and even sudden unexpected death in epilepsy (SUDEP).[51,52]

Secondary prevention: indications

traditionally, initiation of an ASD has been indicated after a 2nd unprovoked ES and/or SE. In contrast, after an

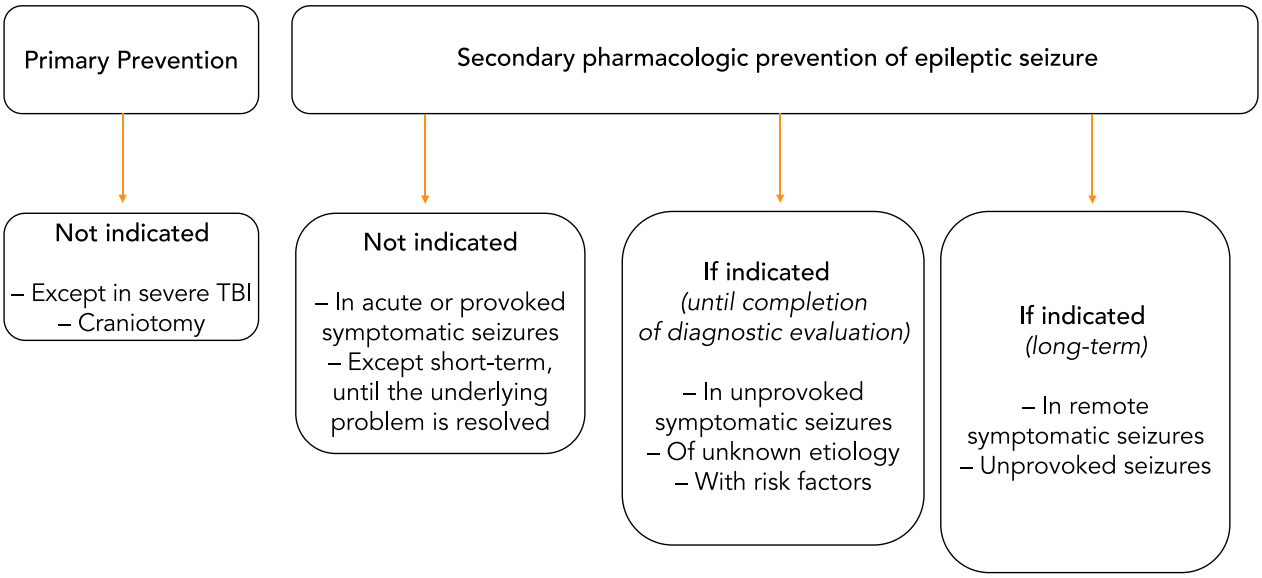

Figure 1. Recommendations for initiating an ASD in a patient without epilepsy.
ASD: anti-seizure drug.

index ES, there is greater controversy. According to recent consensus documents and clinical practice guidelines,[2,12,15-18] preventive treatment is recommended in the following situations (Figure 1):

1. After an acute symptomatic seizure (ASS)—that is, a seizure provoked by a recent CNS structural lesion (< 2 weeks) of traumatic, cerebrovascular, tumoral, or infectious origin; by a toxic problem (acute intoxication or withdrawal); or by severe metabolic disturbance, such as glucose < 36 or > 450 mg/dL, Na < 115 mg/dL, Ca < 5 mg/dL, Mg < 0.8 mg/dL, or Cr > 10 mg/dL, or autoimmune diseases during an active phase.

2. After a remote symptomatic seizure (RSS)—unprovoked, but associated with chronic or residual structural CNS abnormalities, such as postictal encephalomalacia, postoperative changes, chronic subdural hematomas, primary neoplasms or metastases, neurodegenerative or infectious diseases (eg, calcified granulomas due to neurocysticercosis), and in HIV infection in the absence of opportunistic CNS infection or severe metabolic disturbance.

3. After a seizure of indeterminate etiology (formerly cryptogenic or idiopathic) when focal signs are present after the event—eg, Todd's paralysis—and in the presence of risk factors such as non–tonic-clonic onset, congenital or acquired deficits, extremes of age not associated with febrile illness, and abnormal complementary tests (EEG or neuroimaging).

Based on the above—and always individualizing—initial preventive treatment would not be indicated in a young adult without significant comorbidity who presents with a first generalized tonic–clonic seizure, no focal neurological signs, and no significant abnormalities on complementary tests, apart from a resolved toxic–metabolic problem.

Patient with decompensated epilepsy in the emergency department

Care in the ED for patients with decompensated epilepsy usually involves seizures of habitual semiology and frequency, often associated with non-adherence. Treatment interruption within the prior 24 hours is a criterion for high-risk ESs.[4] Common precipitants include sleep deprivation, fever, menstruation, stress, and strobe light. Substances such as alcohol, cocaine, amphetamine derivatives, caffeine, or unknown agents,[53] and drugs such as penicillin-class antibiotics, imipenem or quinolones, isoniazid, chloroquine, opioids (eg, pethidine, tramadol, codeine, fentanyl), acetylcholinesterase inhibitors (eg, donepezil, galantamine, rivastigmine), H1 antihistamines, lidocaine, propranolol, typical antipsychotics and classic antidepressants, lithium salts, or local anesthetics can lower the seizure threshold.[54]

From a practical standpoint, we distinguish decompensations due to seizure recurrence (efficacy) from those due to ASD adverse reactions (safety). Usual clinical scenarios and reasonable decisions are as follows,[2,15-18] (Figure 2):

- ES of habitual semiology and frequency: Conservative approach—maintain and/or restart the usual treatment, avoid triggers (stress, toxic habits, sleep deprivation), and ensure adherence to the habitual ASD.
- Increased frequency of ESs with habitual semiology: in patients with poor adherence, restart the usual regimen. In patients with good adherence, dose adjustment generally does not rely on therapeutic drug monitoring, which is typically available only for VPA (50–100 mg/L), CBZ (4–12 mg/L), DPH/phenytoin (10–20 mg/L), and phenobarbital (10–40 mg/L). Thus, increase doses of current ASDs if on mid-range doses or within range; add a new ASD if already on maximal or supratherapeutic doses.
- Adverse reactions (ARs) to ASDs as the reason for consultation: dose-dependent pharmacologic ARs with neu-

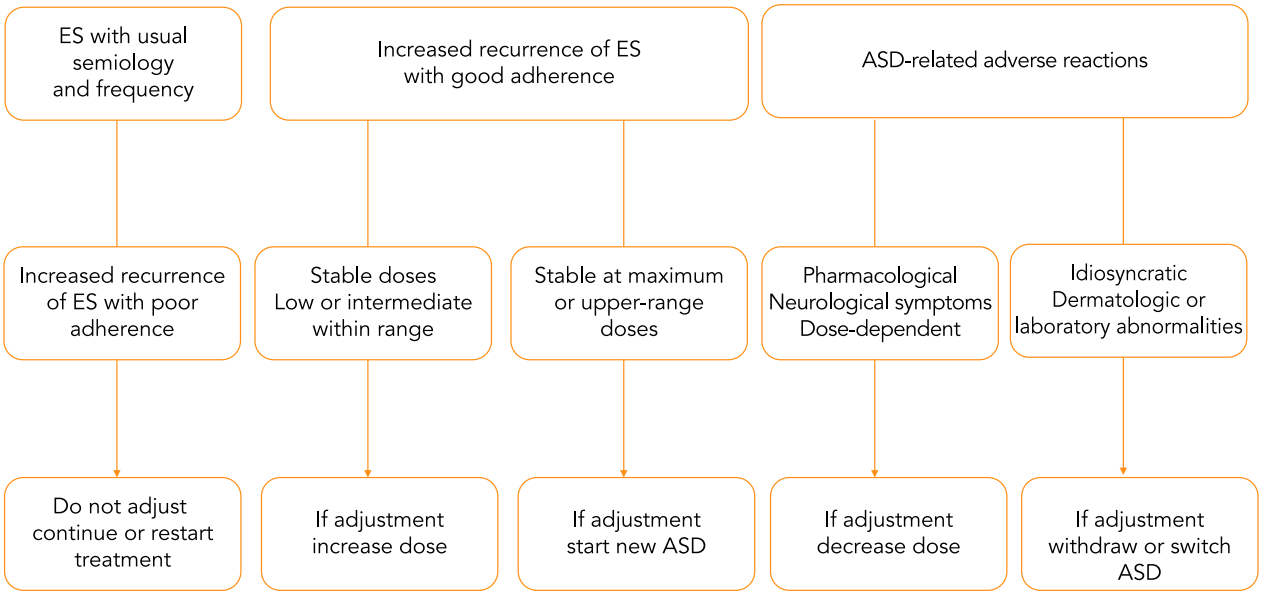

Figure 2. Recommendations for ASD adjustment in a patient with decompensated epilepsy.
ES: epileptic seizure; ASD: anti-seizure drug.

rologic symptoms (dizziness, ataxia, dysarthria, diplopia, blurred vision, asthenia, mood changes) improve by reducing the dose and slower therapeutic titration. Idiosyncratic ARs include dermatologic (usually mild rash, but potentially Stevens–Johnson syndrome) and systemic reactions (eg, agranulocytosis, toxic hepatitis, hypersensitivity syndromes). These dose-independent ARs require immediate withdrawal of the offending ASD. Another possible AR is paradoxical seizure worsening in any epilepsy type, or, in idiopathic generalized epilepsy, the emergence of absences or recurrent myoclonus when using a sodium-channel–blocking ASD.

Finally, the clinical question may arise whether ASDs can be withdrawn in ES-free patients for years but at risk of complications (eg, an older adult on a barbiturate). According to the ILAE, epilepsy may be considered resolved after 10 years seizure-free, with at least the last 5 years off medication.[35] Even so, a general recommendation is not to discontinue treatment unless due to toxicity.

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ADDENDUM

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