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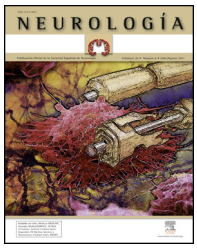

CONSENSUS STATEMENT

The Spanish Society of Neurology's official clinical practice guidelines for epilepsy☆

J.M. Mercadé Cerdá[a,*], M. Toledo Argani[b], J.A. Mauri Llerda[c], F.J. López Gonzalez[d], X. Salas Puig[b], J. Sancho Rieger[e]

[a] *Hospital Regional Universitario Carlos Haya, Málaga, Spain*
[b] *Hospital Universitari Vall d'Hebron, Barcelona, Spain*
[c] *Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain*
[d] *Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, A Coruña, Spain*
[e] *Consorcio Hospital General Universitario, Valencia, Spain*

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Abstract Previous official clinical practice guidelines (CPGs) for epilepsy were based on expert opinions and developed by the Epilepsy Study Group of the Spanish Society of Neurology (GE-SEN).

The current CPG in epilepsy is based on the scientific method, which extracts recommendations from published scientific evidence. Reducing variability in clinical practice through standardisation of medical practice is its main function.

Scope and objectives: This CPG focuses on comprehensive care for individuals affected by epilepsy as a primary and predominant symptom, regardless of the age of onset and medical policy.

Methodology: (1) Creation of a working group of GE-SEN neurologists, in collaboration with neuropediatricians, neurophysiologists and neuroradiologists. (2) Identification of clinical areas to be covered: diagnosis, prognosis and treatment. (3) Search and selection of the relevant scientific evidence. (4) Formulation of recommendations based on the classification of the available scientific evidence.

Results: The CPG contains 161 recommendations of which 57% were established by consensus between authors and publishers, due to significant lack of awareness of this disorder in many fields.

Conclusions: This epilepsy CPG formulates recommendations based on explicit scientific evidence as a result of a formal and rigorous methodology, according to the current knowledge in the pre-selected areas.

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* Corresponding author.
E-mail address: juanmercade@gmail.com (J.M. Mercadé Cerdá).

This paper includes the CPG chapter dedicated to emergency situations in seizures and epilepsy. These may present as a first seizure, an unfavourable outcome in a patient with known epilepsy, or status epilepticus (SE) as the most severe manifestation.

PALABRAS CLAVE
Guía de práctica clínica en epilepsia;
Urgencias en crisis epilépticas;
Primera crisis epiléptica;
Evolución desfavorable de una epilepsia;
Estados epilépticos

Guía oficial de la Sociedad Española de Neurología de práctica clínica en epilepsia

Resumen Las anteriores Guías oficiales de práctica clínica en epilepsia elaboradas por el Grupo de Estudio de Epilepsia de la Sociedad Española de Neurología (GE-SEN) estaban basadas en la opinión de expertos.

La actual Guía de práctica clínica (GPC) en epilepsia se basa en el método científico que extrae recomendaciones a partir de evidencias científicas constatadas. Su principal función es disminuir la variabilidad de la práctica clínica a través de la homogeneización de la práctica médica.

Alcance y objetivos: Esta GPC se centra en la atención integral de personas afectadas por una epilepsia, como síntoma principal y predominante, independiente de la edad de inicio y ámbito asistencial.

Metodología: 1) Constitución del grupo de trabajo integrado por neurólogos del GE-SEN, con la colaboración de neuropediatras, neurofisiólogos y neurorradiólogos; *2)* determinación de los aspectos clínicos a cubrir: diagnóstico, pronóstico y tratamiento; *3)* búsqueda y selección de la evidencia científica relevante; *4)* formulación de recomendaciones basadas en la clasificación de las evidencias científicas disponibles.

Resultados: Contienen 192 recomendaciones. El 57% son de consenso entre autores y editores, como consecuencia del desconocimiento en muchos campos de esta patología.

Conclusiones: Esta GPC, en epilepsia, con una metodología formal y rigurosa en la búsqueda de evidencias explícitas donde ha sido posible, formula recomendaciones extraídas de las mismas.

En este artículo incluimos el capítulo de la GPC dedicado a situaciones de urgencia en crisis epilépticas y epilepsia, que pueden presentarse como una primera crisis epiléptica, una evolución desfavorable en un paciente con una epilepsia conocida o en su forma más grave como un estado epiléptico.

Introduction

Epilepsy refers to a heterogeneous array of highly prevalent illnesses, and it is regarded as one of the most common reasons for neurological consultation. Epilepsy may be defined as a brain disorder characterised by a long-term predisposition to epileptic seizures (ES), and by the neurobiological, cognitive, psychological, and social consequences of that disorder. Diagnosis must be preceded by at least one ES. This is one of the diseases with the greatest impact on patients' quality of life.

The Epilepsy Study Group of the Spanish Society of Neurology (GE-SEN) has published two previous editions of the official guidelines for the diagnosis and treatment of epilepsy. These guidelines were fundamentally based on expert opinion. The current guidelines, drawn up during 2012, are based on the scientific method, which uses confirmed evidence to formulate recommendations.

This study group comprises 47 epilepsy experts, including neurologists, neurophysiologists, neuroradiologists, and paediatric neurologists. The Guidelines were coordinated by five editors under a general director.

Recommendations for searching and selecting applicable scientific evidence are described below.

1. Selective keyword search on PubMed-MEDLINE, using scientific evidence filters to select meta-analyses and controlled clinical trials.
2. Other search engines used to gather evidence:
   - Tripdatabase (www.tripdatabase.com).
   - Cochrane Library/Cochrane Library Plus (http://www.update-software.com/Clibplus/Clibplus.asp).
   - Search engines for treatment data: DARE (http://www.crd.york.ac.uk/crdweb).
   - For prognoses and aetiology: EMBASE (http://www.embase.com).
3. Information from other clinical practice guidelines (CPGs) or recommendations by medical societies: American Academy of Neurology, National Institute for Health and Clinical Excellence, Scottish Intercollegiate Guidelines Network, International League Against Epilepsy, European Federation of Neurological Societies (EFNS), *Guía oficial para el diagnóstico y tratamiento de la epilepsia SEN 2008*, and *Guía andaluza de epilepsia 2009*. The study group adheres to the 2004 EFNS instructions for classifying scientific evidence (Table 1).[1]
4. For prognostic studies, we used a modified version of the evidence grading system promoted by the Oxford Centre for Evidence-Based Medicine.

Table 1 Classification of level of evidence for therapeutic actions

Evidence	
Level 1	Controlled prospective clinical trials with masked outcome assessment in a representative population. Systematic reviews of controlled clinical trials carried out in a representative population. Both types require the following characteristics: (a) Randomised sampling (b) Clearly defined objectives (c) Clearly defined exclusion/inclusion criteria (d) Acceptable accounting for dropouts (e) Baseline characteristics of patients are explicitly described in the text and are similar between groups, or any differences have been statistically adjusted.
Level 2	Prospective cohort studies in a representative population with masked outcome assessment and meeting all criteria from (a) to (e). Prospective controlled clinical trials with masked outcome assessment in a representative population, but not meeting one of the criteria from (a) to (e).
Level 3	All other controlled trials in a representative population in which outcome assessment was independent from the treatment administered.
Level 4	Uncontrolled trials, case series, case reports, or expert opinions.
Grades of recommendation	
Grade A	Recommendation definitively effective, ineffective, or dangerous. Requires at least one conclusive level 1 study or two consistent level 2 studies.
Grade B	Recommendation likely to be effective, ineffective, or dangerous. Requires at least one conclusive level 2 study or several consistent level 3 studies.
Grade C	Recommendation that may be effective, ineffective, or dangerous. Requires at least two consistent level 3 studies.
GE-SEN	Recommendation potentially effective, ineffective, or dangerous. This recommendation does not meet minimum requirements for a grade C, but it reflects consensus among contributors to the clinical practice guidelines.

5. Where scientific evidence was lacking, we followed the general instructions in CPGs issued by other medical societies considering that absence of proof should not be considered proof of inefficacy, that is, 'absence of evidence is not evidence of absence.' In such cases, the recommendation is graded by consensus of the medical society itself. In our case, we assigned the recommendation based on consensus of the GE-SEN.

The Guidelines contain a total of 193 recommendations, some of which are expressed as tables or action algorithms. Epilepsy's pathophysiology is unknown, and so is the cause in some cases. Approval of new antiepileptic drugs (AEDs) rests more on administrative than on clinical criteria. The result of this situation is that scientific evidence remains scarce for all areas of epilepsy. This being the case, 57% of the recommendations in these guidelines stem from consensus between authors and editors and not from scientific evidence. They are therefore expressed as GE-SEN recommendations.

In these guidelines, the terminology and classification systems for ES are those established by the Commission on Classification and Terminology of the International League Against Epilepsy in 1989. This is the dominant practice among the sources we reviewed to create these guidelines.[2]

These guidelines were shown to be a good reference tool for clinical practice in neurological consults, emergency departments, and primary care centres during 2013.

The full version of this consensus statement can be viewed on the SEN's webpage, and the journal Neurología is publishing excerpts on epilepsy treatment under the following titles:

- Emergencies in epilepsy and ES.
- Pharmacological treatment of epilepsy (two articles).
- Drug-resistant epilepsy. Non-pharmacological treatments.

Emergencies in epilepsy and ES

Introduction

ES account for about 1% of all emergency department visits. These cases can be categorised as follows[3]:

1. Patients whose seizure is associated with signs or symptoms of acute, systemic, or CNS disease. This type is known as provoked seizure (PS) (or acute symptomatic seizure), and its treatment requires resolving the underlying cause as well as achieving seizure control.
2. Patients with an initial seizure. The cause of an initial seizure cannot be immediately determined in half of all cases.
3. Patients with known epilepsy who experience worsening of the disorder, referring to both increased critical frequency and increased AED tolerance.
4. Patients with prolonged or clustered seizures that are classified as different types of status epilepticus (SE).

Due to their poor prognosis, these conditions require immediate and appropriate treatment.

Classifying symptomatic ES by temporal relationship with the cause

Symptomatic ES are those that arise due to brain insult. There are two types: PS and remote symptomatic seizures (RSS). Provoked or acute symptomatic seizures are those directly caused by, or occurring soon after, a precipitating factor. This factor may be metabolic, toxic, structural, infectious, or inflammatory, and it causes an acute brain event (Table 2). Remote symptomatic ES are caused by pre-existing static or progressive brain lesions. They may appear as isolated events or else recur (epilepsy).

The current International Classification of Epileptic Syndromes[4] places PS among the conditions presenting with ES, but not considered to be epilepsy proper. PS do not require long-term antiepileptic treatment, although short-term treatment may be necessary until the acute condition has resolved.

Scientific evidence for pharmacological treatment of acute symptomatic seizures

- Carbamazepine, phenobarbital (PB), phenytoin (PHT), and valproic acid (VPA), the classic AEDs, are effective for preventing PS in cases of severe traumatic brain injury. PHT effectively prevents PS after craniotomy.[5,6] Level of evidence 1.
- Classic AEDs effectively prevent PS due to traumatic brain injury or craniotomy, contrast material, malaria, or alcohol withdrawal syndrome. They do not prevent RSS or future development of epilepsy due to these causes.[5,6] Level 1.
- Benzodiazepines (BZD) are effective for preventing PS due to alcohol withdrawal.[5,6] Level 1.
- Patients with brain tumours treated with antineoplastic drugs, radiotherapy, or corticosteroid treatment should not take classic AEDs due to interactions or idiosyncratic adverse effects.[6] Level 4.

Patients with an initial tonic-clonic seizure of undetermined cause

Most patients who visit the emergency department due to ES have experienced an initial generalised tonic-clonic seizure (GTCS) whose cause cannot be determined (Fig. 1).

Scientific evidence on treating an initial GTCS

- Most guidelines indicate, based on randomised observational studies, that AED treatment should not be started until the patient experiences a second GTCS of undetermined cause.[7] Level 1.
- Treatment with AEDs reduces risk of recurrence in the short term (months or weeks), but this does not affect the patient's long-term prognosis for seizure remission.[8] Level 1.

Action algorithm for initial GTCS is shown in Fig. 1.

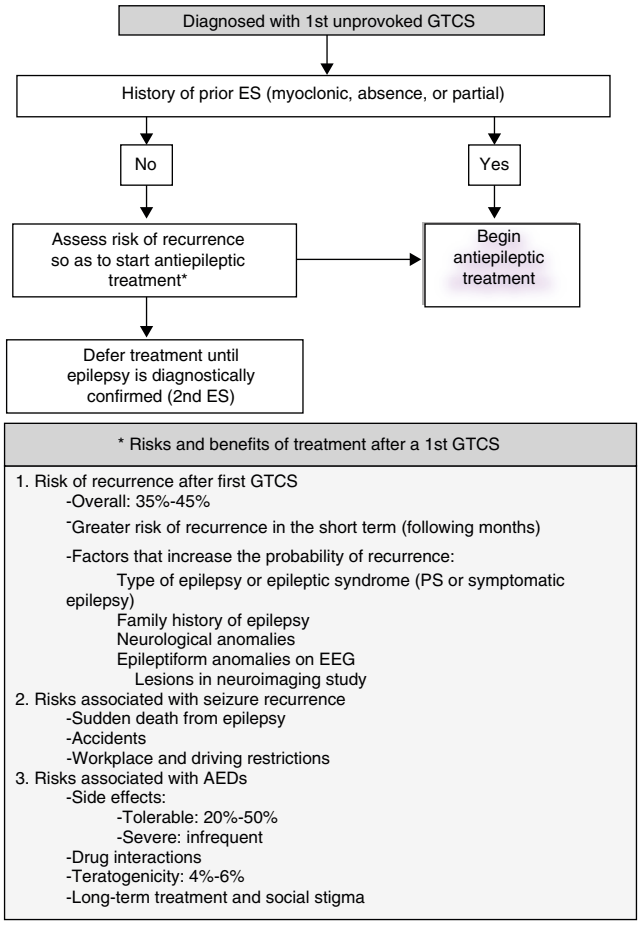


Figure 1 Diagnostic and therapeutic algorithm for use after an initial generalised tonic-clonic seizure (GTCS).

Unfavourable changes in progression of previously diagnosed epilepsy are characterised by either increase in habitual critical frequency or AED intolerance. Emergency action algorithm for this type of clinical situation is shown in Fig. 2.

Patients with clustered or prolonged seizures constitute different types of SE. Status epilepticus is a seizure lasting more than 30 minutes, or a sequence of seizures repeated over more than 30 minutes during which time the patient does not recover the baseline neurological state.[9] There are as many types of SE as there are seizure types. The most common classification system for SE is shown in Fig. 3.

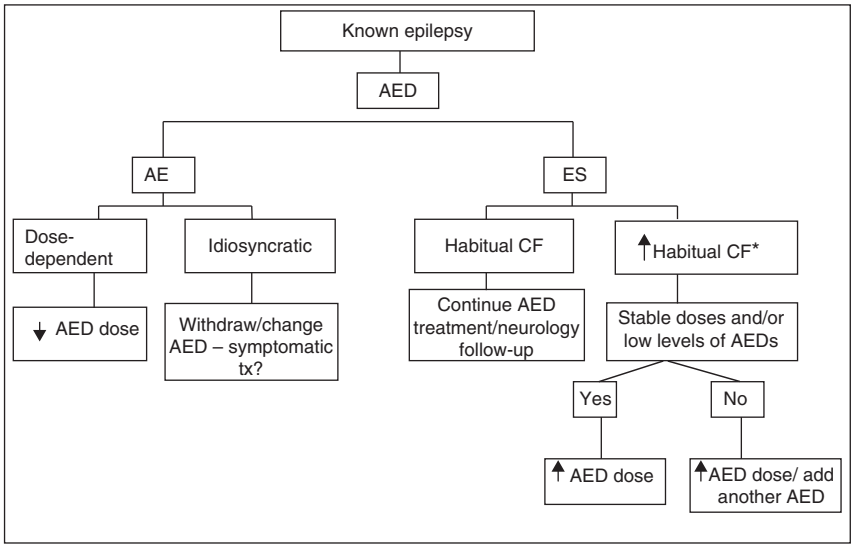
Clinical experience and video-EEG monitoring show that a convulsive seizure that continues beyond 5 minutes gives rise to convulsive SE. Mortality is higher in cases of SE lasting more than 30 minutes.

The literature lists different definitions and classifications of SE for use in clinical practice and treatment.[7,10]

- Convulsive tonic-clonic SE:
  - A generalised, continuous convulsive seizure lasting 5 minutes or longer.
  - Two or more generalised convulsive seizures presenting without the patient regaining consciousness between seizures.

Table 2 Acute symptomatic epileptic crises

Aetiology	Temporal relationships	Observations and exceptions
Head trauma	During the first week	Includes intracranial surgery and subdural haematomas (a longer period may be accepted)
Cerebrovascular disease	During the first week	
Brain tumour	ES as initial symptom	
Neuromeningeal infection: bacterial or viral	During the course of the infection	
Neurocysticercosis	Parasites visible on neuroimaging study	ES due to calcified granulomas are RSS
Malaria	Presence of fever and parasitaemia	
Cerebral tuberculoma	During treatment	ES after effective treatment are RSS
Cerebral abscess	During treatment	ES after effective treatment are RSS
HIV positive	During acute infection or severe metabolic changes	ES in the absence of an opportunistic CNS infection or severe metabolic changes are RSS
Toxic substances	During exposure time	High risk: cocaine, amphetamines, crack, inhalants Low risk: heroin and marijuana
Abstinence	In the period immediately after withdrawal	
Metabolic	During the course of the disorder	Serum levels proposed for PS — Glucose <36 or >450 mg/dL with ketoacidosis — Na <115 mg/dL — Ca <5 mg/dL — Mg <0.8 mg/dL — Cr <10 mg
Fever	Accompanying fever in children without neuromeningeal infection	
Autoimmune diseases	During activation phase	



AED: antiepileptic drug; AE: adverse effects; ES: epileptic seizures

CF: critical frequency ↑increase

* Always assess precipitants and how to correct them

Figure 2 Action algorithm for patients with known epilepsy

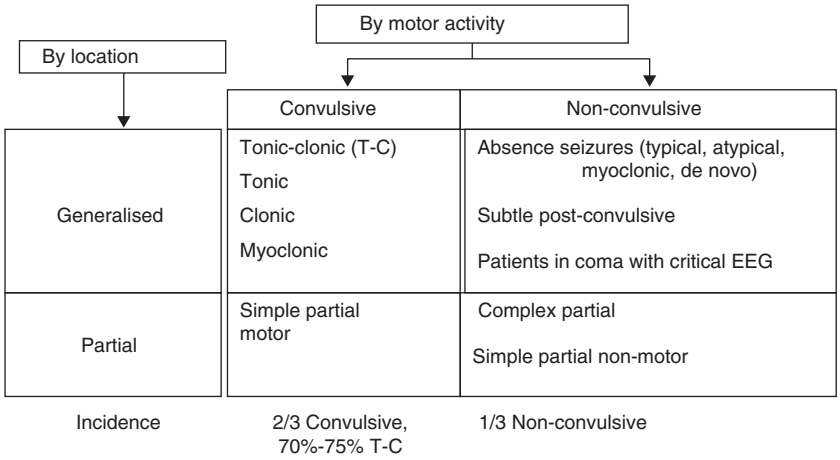


Figure 3 Classification by motor activity, location, and incidence of epileptic syndromes

- Cluster seizure: two or more generalised convulsive seizures in an hour.

- Refractory SE (RSE): continuous SE after treatment with two appropriately chosen and correctly dosed AEDs.
- Non-convulsive SE (NCSE): seizure without recognisable or predominant motor activity and a continuous critical EEG trace. The typical clinical manifestation of this type of SE is decreased level of consciousness.

Anticonvulsant treatment

Initial convulsive SE episode

Clinical response to convulsive SE should initially entail checking vital signs, followed by providing anticonvulsant treatment and treating the cause or other associated problems (Fig. 4).

Most CPGs recommend intravenous (IV) administration of the BZD drugs lorazepam (LZP) or diazepam (DZP) as the first line of treatment for all types of SE.[7,11]

Scientific evidence for initial treatment of convulsive SE

- LZP and DZP are effective for treating convulsive SE.[12] Level 1.
- Non-IV midazolam (MDZ, administered by oral, nasal, intramuscular, or rectal routes) is as effective as IV DZP; oral MDZ is superior to rectal DZP.[13] Level 2.
- Intramuscular MDZ shows similar efficacy to IV LZP as initial prehospital treatment. Level 2.[14]

Loading dose, route of administration, and duration of effect vary for different types of BZD (Table 3).

Established convulsive SE

If the initial BZD treatment, including a second dose, fails to control convulsive SE, a second-line AED must be administered (Table 4).

Scientific evidence for treatment of established convulsive SE

- IV DZP + PHT, PB, and LZP are equally effective for controlling convulsive SE at 20 minutes after perfusion and during the first hour.[12] Level 1.
- IV PHT and VPA, and VPA and LEV are equally effective for controlling convulsive SE at 30 minutes after perfusion and in cases of adverse effects.[10,15] Level 2.
- IV lacosamide (LCM) was shown to be effective by different non-prospective, non-controlled studies and case series for different types of SE. Level 4.[16]
- Most CPGs recommend using LZP (4 mg IV) or DZP (10 mg IV) followed by PHT (18 mg/kg IV) or PB (20 mg/kg IV).[7,11] Level 4.
- Treatment with VPA, LEV, or LCM is indicated in cases of RSE or when PHT is contraindicated, as an alternative to IV PB.[17,18] Level 3. LEV and LCM are not authorised as treatments for SE.

Several randomised clinical trials are currently being carried out to compare the efficacy of PHT, fosphenytoin, VPA, and LEV.[19]

Treatment for the cause of seizures, if known, should be administered simultaneously with anticonvulsants. Systemic complications of SE (fever, metabolic disorders, rhabdomyolysis, etc.) should also be treated at the same time (Table 5).

RSE

There is no consensus on a definition of RSE. The medical literature defines RSE as a seizure lasting more than 60 minutes, or failure of two appropriately employed and properly dosed second-line AEDs.

Steps in treating RSE are as follows:

1. Admit patient to the ICU. Stabilise vital signs. Continue treating or investigating the cause.
2. Maintain treatment with habitual AEDs.
3. Induce medical coma during 24 to 48 hours. There is no evidence that barbiturates (thiopental) are

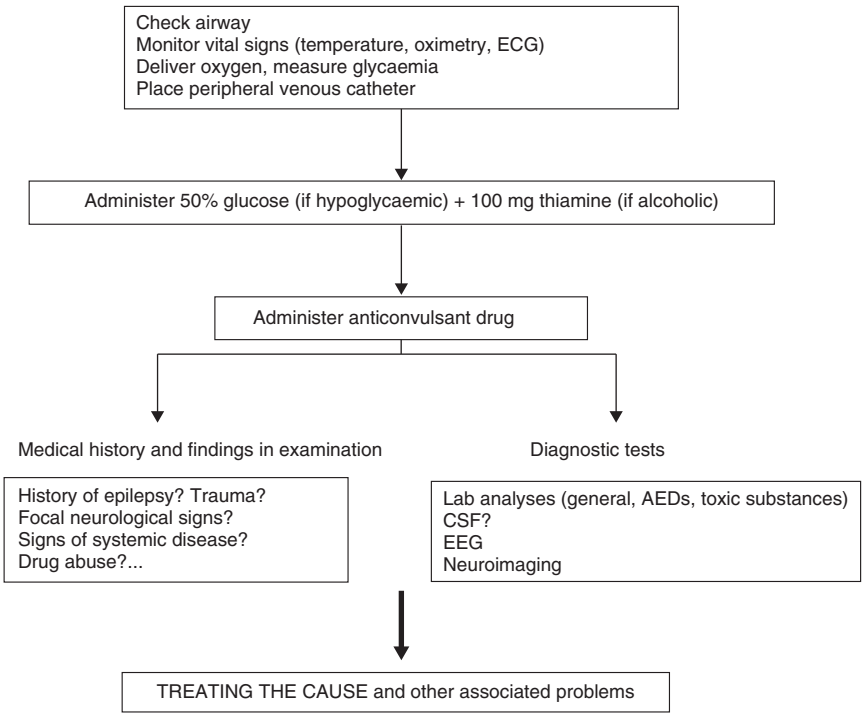


Figure 4 Clinical action plan for convulsive SE

Table 3 IV treatment regimens and benzodiazepine pharmacokinetics in convulsive SE

Benzodiazepines	Adults Initial dose/maximum loading dose	Maximum administration rate	Duration of seizure control	Duration of effect
DZP	5-10 mg/20 mg	2-5 mg/min	1-3 min	10-30 min
CZP	1-2 mg/4 mg	0.2 mg/min	3-10 min	12 h
MDZ	1-5 mg	2 mg/min	1-1.5 min	10-30 min
LZP[a]	2-4 mg/10 mg	2 mg/min	6-10 min	12-24 h

Non-IV treatment regimens: DZP rectal route, 10-30 mg; MDZ oral/nasal/intramuscular, 5-10 mg.
CZP: clonazepam; DZP: diazepam; LZP: lorazepam; MDZ: midazolam.
[a] Not marketed in Spain (IV).

superior to non-barbiturates (propofol, MDZ) for inducing a medical coma.[10,11,20] Level 4. The choice of treatment depends on associated comorbidities, pharmacokinetics, and adverse effects.

4. Withdraw drugs used to induce coma in 12 to 24 hours if clinical symptoms and EEG indicate SE resolution (monitoring).
5. Start/continue administering long-term AED treatment.

Table 4 IV treatment regimens and AED pharmacokinetics in convulsive SE

AED	Initial dose	Duration of seizure control	Maintenance dose	AED level in SE
PHT	15-20 mg/kg (50 mg/min)	10-30 min	4-6 mg/kg/day (12 h initial dose)	25-40 μg/mL
VPA	25-45 mg/kg (4—6 mg/kg/min)	10-15 min	0.5-1 mg/kg/h (1/2 h initial dose)	50-150 μg/mL
PB	10-20 mg/kg (100 mg/min)	20-30 min	2-4 mg/kg/day (12-24 h initial dose)	15-40 μg/mL
LEV[a]	20 mg/kg 250-3000 mg bolus	15 min	20-30 mg/kg/24 h (12 h after initial dose)	25-60 mg/L
LCM[a]	200-400 mg (15-60 min)	3-5 min	200 mg/12 h (12 h after initial dose)	Unknown

AED: antiepileptic drug; LCM: lacosamide; LEV: levetiracetam; PB: phenobarbital; PHT: phenytoin; VPA: valproic acid.
[a] Product leaflet states that product is not indicated as treatment for SE.

Table 5 Instructions for IV treatment and pharmacokinetics for anaesthetics as treatment for convulsive SE

Drug	Initial dose	Infusion rate	Maintenance dose	Level in SE
Midazolam	0.1-0.2 mg/kg bolus	4 mg/2 min	0.1-0.4 mg/kg/h	0.2-1 μg/mL
Propofol	3-5 mg/kg bolus	Slow	5-10 mg/kg/h	Unknown
Thiopental	2-3 mg/kg bolus	30 s	3-5 mg/kg/h	25-50 μg/mL
Pentobarbital[a]	5-15 mg/kg	Slow	0.5-3 mg/kg/h	Unknown

[a] Not marketed in Spain.

Table 6 General list of recommendations for treating epilepsy in the emergency department

Recommendations//PS prophylaxis and treatment		Grade of recommendation
Administering AED for the primary prevention of PS is only indicated for patients with severe head trauma, craniotomy, and alcohol withdrawal syndrome.		A
Do not administer AED to patients with brain tumours, CNS infections, or acute toxic or metabolic disorders who have not experienced seizures.		A
Recommend second generation AEDs that are not metabolised in the liver in patients with PS caused by brain tumours during radiotherapy, or during corticosteroid or antineoplastic treatment.		GE-SEN
Treatment with AEDs for primary or secondary PS prevention should not be extended beyond the time needed to resolve the cause.		A
Recommendations//after first GTCS		Grade of recommendation
A patient starting treatment with AEDs must be informed about risks and benefits, and personal preferences should be taken into account.		GE-SEN
Start treatment with AEDs if patient has a history of other types of ES.		B
Recommendations//SE treatment		Grade of recommendation
	Initial pharmacological treatment for any prolonged seizure or SE episode should be BZD.	A
	Intravenous PHT and PB should be used if status epilepticus is not controlled with BZD.	A
Convulsive SE	Intravenous VPA and LEV should be used for status epilepticus if PHT is contraindicated.	B
	VPA, LEV, and LCM can be used to treat status if PHT is contraindicated, as an alternative to IV PB, or in refractory SE.	C
Refractory SE	Selection of drugs used to induce a medical coma for refractory SE should be based on the experience or protocols of the responsible ICU.	GE-SEN
Non-convulsive SE	Aggressive treatment is not recommended in patients who are not in deep coma since their prognosis is good.	GE-SEN

6. Treat cause and any complications.

If RSE persists after 24 hours of starting anaesthetic treatment, or if SE recurs with reduction or withdrawal of anaesthesia (a clinical state called 'super-refractory' SE by some authors), other types of non-anaesthetic treatment should be attempted. These include magnesium sulphate, pyridoxine (in children), steroids, immunoglobulins, plasmapheresis, hypothermia, ketogenic diet, electroconvulsive therapy, neurosurgery for lesion-induced SE, and vagus nerve stimulation; treatment sequences vary depending on the cause and according to different authors.[20] Level 4.

NCSE

This definition is based on absence of manifest motor activity with an indicative EEG pattern. If there is a clinical suspicion, the diagnosis is confirmed by EEG. Lack of unified EEG terminology makes it more difficult to classify cases of NCSE.

Most authors use electroclinical data to classify NCSE into two groups: with and without coma/stupor.

The group without coma/stupor is further subdivided into SE with generalised onset (absence SE: typical, atypical, or myoclonic), focal onset (NCSE with or without altered consciousness, aphasia, etc.), and unknown origin (autonomic NCSE).[21]

There is no high-level evidence regarding which treatment to choose for each type.

For non-hospitalised patients with a prolonged history of confusional states, experts recommend treatment with BZD, preferably by the oral route.[7]

Treatment for patients in coma following a convulsive SE episode (subtle NCSE) resembles that for RSE cases.

Critical activity can be seen on the EEG trace in 20% to 30% of the cases in which the patient is comatose and his/her situation is critical due to a wide range of serious causes (anoxic brain injury after cardiac arrest, head trauma, severe intoxication, etc.). The underlying cause, which determines prognosis, has to be treated in these cases, and non-sedating AEDs must be added to the treatment regimen.[12]

We have listed recommendations for a variety of clinical situations that may be observed in the emergency department (Table 6).

Conflicts of interest

The authors declare no conflicts of interest.

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