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CRITICAL REVIEW

Clinical practice guidelines on the management of status epilepticus in adults: A systematic review

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Abstract

Objective: Status epilepticus (SE) is the second most common neurological emergency in adults. Despite improvements in the management of acute neurological conditions over the last decade, mortality is still durably high. Because a gap has emerged between SE management based on clinical practice guidelines (CPGs) and actual clinical practice, we conducted a systematic review of CPGs, assessing their quality, outlining commonalities and discrepancies in recommendations, and highlighting research gaps.

Methods: We searched the PubMed and EMBASE databases and other gray literature sources (nine among guideline registries, evidence-based medicine databases, point-of-care tools; seven websites of governmental organizations and international neurologic societies) in December 2021 (updated in November 2023). The units of analysis were CPGs that included recommendations on the diagnostic and/or therapeutic management of SE in adults. The quality of the CPGs was assessed using the AGREE II tool.

Results: Fifteen CPGs were included. The "Applicability" domain was assigned the lowest median score of 10%. The domains "Stakeholder Involvement", "Rigor of Development," and "Editorial Independence" were as well generally underrated. Recommendations on general and diagnostic management and on organizational interventions were fragmented and scattered. Recommendations on pre-hospital and hospital treatment of early-onset and refractory SE were broadly agreed, whereas there was less agreement on the treatment model and medications for established SE and super-refractory SE.

Significance: The CPGs for the management of SE developed in recent years are flawed by several methodological issues and discrepancies in the coverage of important topics. The gap between CPG-based management of SE and actual clinical practice may be due in part to the inherent limitations of the CPGs produced so far.

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KEYWORDS
anticonvulsants, electroencephalography, guideline adherence, practice guidelines as topic, status epilepticus

1 | INTRODUCTION

"Status epilepticus (SE) is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures [... and ...] which can have long-term consequences [...]."[1] SE is the second, time-dependent,[1] neurological emergency in adults, affected by significant deficits[2] and high mortality.[3] Thirty-day mortality in adults is about 16%, with a high variability (from 2% to 39%) that could be only partly explained by a different distribution of known prognostic variables (mainly age and etiology) and methodological heterogeneity among studies.[3,4] Other unknown factors are likely involved, and it is particularly interesting that mortality is still durably high.[3,4] This stability could be explained by two opposing trends, namely, the progressive aging of susceptible patients and the improved management of acute neurological conditions (e.g., new anti-seizure medications [ASMs][5]). A further factor could be the gap between SE management based on clinical practice guidelines (CPGs) and the actual clinical practice, which has been reported consistently over the decades and has been shown to have an impact on patient outcomes in some settings.[6–11] Several studies have reported that clinicians often do not follow recommendations[10] and that deviations from CPGs include delayed administration of ASMs and misuse of benzodiazepine.[10–12]

CPGs are "statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[13] The expected benefits of CPGs are influenced by many factors, including their methodological quality, organizational issues, and physician and patient factors.[14,15] Another crucial issue is the applicability of the CPGs, that is, providing users with tools for clinical implementation.[16] Among the other domains of CPG quality ("Scope and Purpose", "Stakeholder involvement", "Rigor of Development", "Clarity and Presentation", "Editorial Independence") according to the AGREE II assessment tool,[16] "Applicability" is one of the most neglected and low-scoring,[17,18] and this limitation has not changed over the past two decades.[19]

Neurological scientific societies are making extraordinary efforts to develop and implement good evidence-based practice guidelines,[20–23] so we believe that information to improve future guidelines is critical.

Key points

- This systematic review identified 16 international clinical practice guidelines on the management of status epilepticus in adults, published since 2010.
- The quality of the guidelines was assessed using the AGREE II tool. Applicability, Stakeholder Involvement, and Rigor of Development were the domains that received particularly low median scores (10%, 47%, and 59%, respectively).
- Recommendations on general management were fragmented. Organizational aspects were considered by very few guidelines.
- Recommendations provided good coverage of drug treatment for early and refractory status epilepticus, with substantial agreement among the guidelines. Less agreement was observed on drugs for established or super-refractory status epilepticus.
- This study provides suggestions for the development of future guidelines on status epilepticus, such as involving a wider audience of stakeholders in task forces, using well-established methodological tools, and providing decision-support tools and indicators for auditing guideline implementation.

In 2016, the International League Against Epilepsy (ILAE) Epilepsy Guidelines Task Force published a systematic review including 63 guidelines covering every aspect of epilepsy health care.[24] The task force found some gaps in topics (e.g., related to extreme ages, such as infants and the elderly) and heterogeneity in methodological quality, with low scores especially for the Applicability domain. Seven CPGs on SE were found in that review, but no specific data were reported.

Assuming that the quality and characteristics of CPGs may play a role in the limited implementation of best practices on the management of SE in adults, the aims of this systematic review were: (1) to assess the quality

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of CPGs, assuming that the Applicability domain may be particularly overlooked; (2) to outline commonalities and discrepancies in recommendations; and (3) to highlight research gaps in the management of SE.

2 | METHOD

This systematic review followed the methodology by Johnston et al.[25] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.[26] Protocol was registered with PROSPERO database (CRD42022314153) and published (10.5281/zenodo.6363324).

2.1 | Inclusion criteria

The unit of analysis was CPG, which included recommendations on the diagnostic and therapeutic management of SE in adults. We defined inclusion and exclusion criteria according to the PICAR (Population & Clinical Areas, Interventions, Comparators, Attributes of CPGs, and Recommendation characteristics) framework for systematic reviews of CPGs (Table S1).[25] To ensure clinical relevance and minimal quality, eligibility was limited to CPGs issued by national health authorities, national or international professional organizations or societies, reporting a methodology of CPG development, published since 2010, without language, sex, ethnicity, or setting restrictions. We excluded CPGs addressing SE in children. The following clinical subgroups were outlined: SE with prominent motor phenomena ("convulsive" SE [CSE]), SE without prominent motor phenomena ("non-convulsive SE" [NCSE]), refractory SE (RSE), and super-refractory SE (SRSE). The interventions of interest were procedures/tests for diagnosis of the etiology of SE, procedures/tests for diagnosis of seizure condition, and any treatment of SE (excluding etiologic treatments). These elements were framed, if possible, by the duration of SE and setting (pre-hospital, in-hospital).

2.2 | Data sources and searches

In December 2021 (update November 2023), we searched PubMed and EMBASE databases, guideline registries (5), EBM databases (2), point-of-care tools (2), websites of governmental organizations (3), and websites of international neurologic societies (4) (details in Supplementary Information). Finally, we searched Google for additional records using "status epilepticus" and "guideline" as search terms, sifting through the first 100 results. Reference lists of all retrieved CPGs were scanned.

2.3 | Study selection and data extraction

Two researchers independently screened the titles and abstracts of identified records for eligibility and checked for inclusion criteria the full text of eligible documents. One researcher extracted metadata (title, year, developer, country of origin, topic/scope, development method/quality grading system). Two researchers extracted the text of the recommendations of interest. Disagreements were resolved by discussion. For all included CPGs, we also retrieved any associated companion article (e.g. methodology supplements and background documents) or relevant accompanying online information.

2.4 | Quality assessment

Three researchers independently assessed the quality of the CPGs using the AGREE II tool,[16] which covers 23 items in the domains of "Scope and Purpose", "Stakeholder Involvement", "Rigor of Development", "Clarity of Presentation", "Applicability", and "Editorial Independence". Each item was scored on a 7-point Likert-type scale from 1 (strongly disagree) to 7 (strongly agree). A final quality score for each domain was calculated according to the AGREE II user's manual and provided on a percentage scale.[16]

2.5 | Data synthesis, and analysis

Three researchers, by means of thematic analysis[27] and an iterative independent process, defined the following final agreed set of topics to classify recommendations: target audience, pre-hospital management of early SE, hospital management of early SE, hospital pharmacological treatment of early and established SE, management of RSE/SRSE, and specific issues of other than CSE forms.

We reported in a table the main characteristics of the included CPGs. We presented AGREE II scores for each CPG and for each individual domain, then for each domain in total. The six domains were ranked according to the mean score, and the ranking was used to focus on the most neglected domains and to prioritize methodological suggestions for future CPGs. To assess the impact of possible

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variability in the ratings of the three assessors, we ranked each domain according to the mean score, for each assessor.

A synopsis for each topic was constructed to compare and summarize recommendations. The proportion of coverage by CPGs was calculated for each topic. The quality of evidence supporting recommendations was extracted. To facilitate a comparison of the quality of evidence on the basis of recommendations, the rating systems of all CPGs were converted into a common comparable system[28] (Table S2).

3 | RESULTS

The search strategy produced 498 records; 30 documents were selected for full-text review and 17 documents corresponding to 16 CPGs met inclusion criteria (Figure 1; Tables 1 and S2). The excluded full texts are listed in Table S3, with the reasons for exclusion. Eight CPGs were developed in Europe,[e1,e4,e8,e10,e12–e15] five in the United States,[e2,e5–e7,e9] two in South America,[e3,e11] and one in Asia.[e16] To assess the quality of evidence upon which recommendations were produced (Table S2), four CPGs used adaptations the Grading Recommendations, Assessment, Development and Evaluation (GRADE) system,[e4,e13,e14,e16] two American Academy of Neurology (AAN) system,[e7,e12] two Scottish Intercollegiate Guidelines Network (SIGN) system,[e3,e10] one American College of Emergency Physicians system,[e9] and one American Heart Association system,[e2] whereas four guidelines[e1,e5,e8,e15] did not identify their system by name, and finally two CPGs did not use any system.[e6,e11]

3.1 | Quality assessment of included guidelines

The quality appraisal by AGREE II domain scores is provided in Figure 2 for the whole group and in Table 2 for each individual CPG.

"Applicability" was assigned the lowest median score of 10% (range 3–86%; mean 18.7%, SD 21.4), followed by "Stakeholder Involvement" (median 47%; range 15–94%; mean 48.1, SD 24.0), "Rigor of Development" (median 59%; range 18–90%; mean 56.1, SD 21.6), "Editorial Independence" (median 63%, range 11–97%; mean 60.6, SD 24.9), "Scope and Purpose" (median 66%; range 44–83%; mean 66.6%, SD 12.0), and "Clarity of Presentation" (median 80%; range 52–89%; mean 75.6%, SD 12.8). The assessors individually ranked the domains in the same order (see Table S4).

Only one CPG[e14] scored ≥70% on all six domains, and four[e1,e3,e6,e11] ranked below 70% on all domains.

3.2 | Recommendations on management of status epilepticus

Comparing the declared scope of each CPG, the topics covered by recommendations are shown in Table 3.

3.2.1 | Pre-hospital management of early SE

Recommendations on at least one general management intervention were reported in 8 of 12 CPGs, with sparse indications (Table 4A). Only two CPGs recommended definition and reporting the time of seizure onset. Information on target condition, target health professionals, and timing was reported in a minority of CPGs. Eleven of 12 CPGs gave recommendations on drug treatment of early SE: first choice treatment is midazolam for 11 CPGs followed by diazepam (7) and lorazepam (6).

3.2.2 | Hospital management of early SE

Twelve of 13 CPGs gave recommendations on at least one general management intervention, with sparse indications on laboratory test and protection of airway/breathing support/intubation (Table 4B,C). Only one CPG recommended the definition of the time of seizure onset. Eleven of 13 CPGs gave recommendations on at least one etiologic investigation (nine focusing on imaging, six lumbar puncture, and five on laboratory tests). Eleven of 12 CPGs provided recommendations regarding diagnostic electroencephalography (EEG) and included guidance on when NCSE should be suspected.

Timing for performing EEG was suggested in seven CPGs with different delays (from 1 to 24 h) and it was recommended as prolonged or continuous by eight CPGs. Minimal duration (24–48 h) was suggested in three CPGs. No CPG reported specific guidance for the management of SE with intra-hospital onset.

3.2.3 | Hospital pharmacological treatment of early and established SE

Seven CPGs applied a treatment framework based both on temporal criteria and treatment failure to decide subsequent treatments after the first line of treatment; four CPGs applied only a treatment failure framework; two CPGs applied only a temporal framework (Table 4D).

Benzodiazepines were recommended as first choice for early SE by all CPGs. The specific benzodiazepines most recommended were intravenous lorazepam (12) or diazepam (8) or midazolam (8). Repeated doses of

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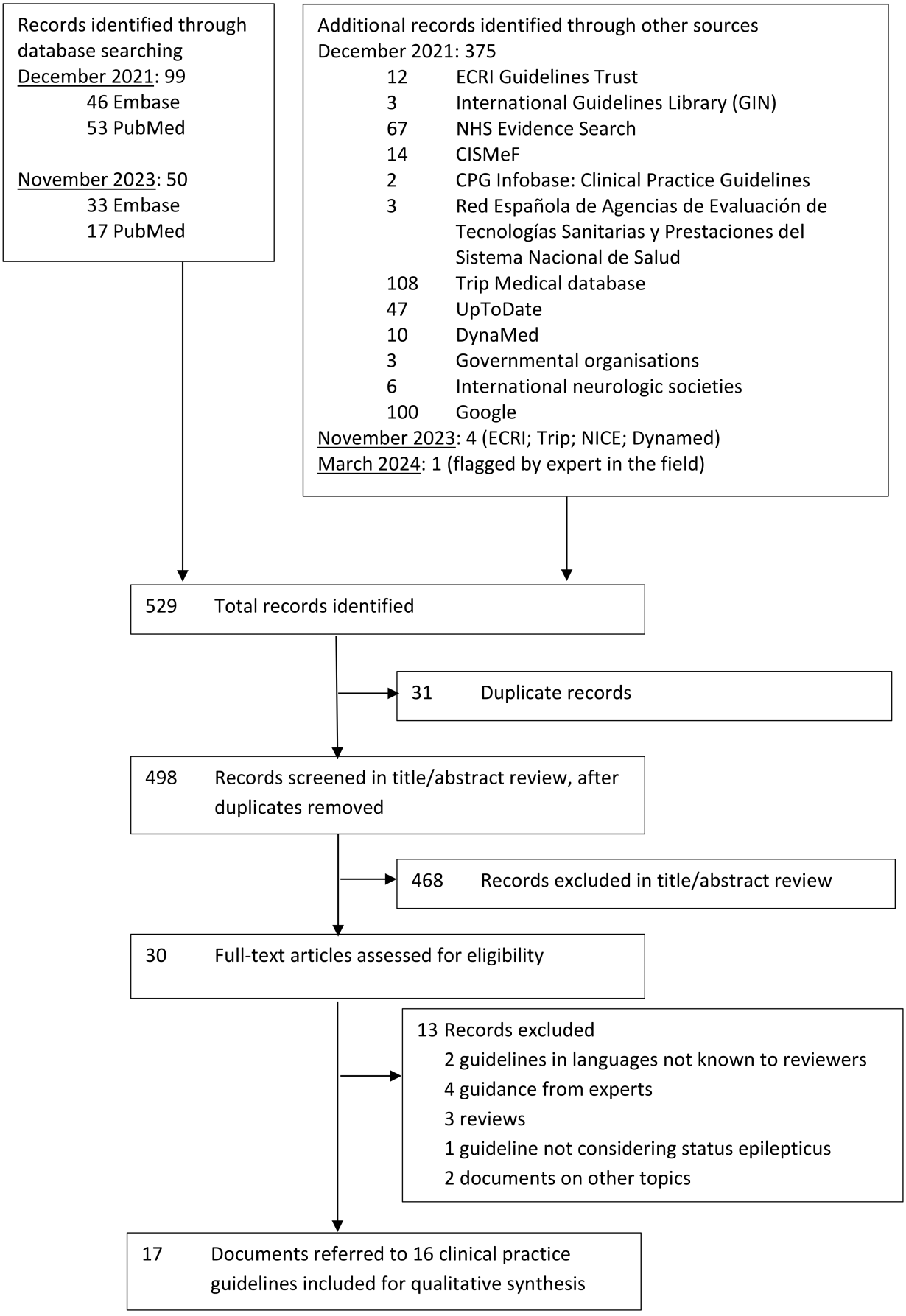

FIGURE 1 PRISMA flow diagram of December 2021 and November 2023 searches (temporal limit 2010).

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TABLE 1 Characteristics of the 16 included clinical practice guidelines on the management of status epilepticus in adults.

Guideline/year	Developer	Country	CPG scope
EFNS 2010[e1]	European Federation of Neurological Societies	International (Europe)	Treatment of SE in adults
NCCS 2012[e2]	Neurocritical Care Society	USA	Evaluation and treatment of SE
SNA 2013[e3]	Argentinian Society of Neurology	Argentina	Diagnosis and treatment of SE in adults
ESICM 2013[e4]	European Society of Intensive Care Medicine	International (Europe)	Use of EEG monitoring in critically ill patients (including SE)
ACEP 2014[e5]	American College of Emergency Physicians	USA	Evaluation and management of adult patients presenting to the emergency department with seizures (including SE)
ACNS 2015[e6]	American Clinical Neurophysiology Society	USA	Continuous EEG in critically ill children and adults (including SE)
AES 2016[e7]	American Epilepsy Society	USA	Treatment of convulsive SE in children and adults
SEN 2016[e8]	Spanish Society of Neurology	Spain	Diagnosis and treatment of the epilepsies in adults and children (including SE)
EMSAC 2017[e9]	Emergency medical services Medical Directors Association of California	California (USA)	Prehospital care for the adult and pediatric seizure patient (including SE)
SIGN 2018[e10]	Scottish Intercollegiate Guidelines Network	Scotland	Diagnosis and treatment of epilepsy in adults (including SE)
JSN 2018[e16]	Japanese Society of Neurology	Japan	Diagnosis and treatment of the epilepsies in adults and children (including SE)
ACN 2019[e11]	Colombian Neurology Association	Colombia	Treatment of SE in children and adults
LICE 2020[e12]	Italian Legue Against Epilepsy	Italy	Diagnosis and treatment of SE in adults
SRLF/SFMU 2020[e13]	French Resuscitation Society, French Society of Emergency Medicine	France	Management of SE in the prehospital setting, in the emergency department and in intensive care unit
NICE[a] 2012/2022[e14]	National Institute for Health and Care Excellence	United Kingdom	Diagnosis and treatment of the epilepsies in adults and children in primary and secondary care (including SE)
DGN/OGN 2021[e15]	German Society of Neurology, Austrian Society of Neurology	Germany, Austria	Diagnosis and treatment of SE in adults

[a]NICE has published two documents that cover topics related to the management of status epilepticus in different ways. We decided to include both documents, considering that recommendations related to topics covered in only one of the two documents or the most up-to-date recommendations related to topics covered in both documents.

benzodiazepines were recommended in case of no response by eight CPGs. One CPG explicitly recommended the use of an adequate single full dose rather than multiple smaller doses.[e7]

For established SE, ASMs were the first choice according to almost all CPGs. The specific ASMs most recommended were intravenous valproic acid (7), phenytoin/fosphenytoin (10), phenobarbital (5), and levetiracetam (4).

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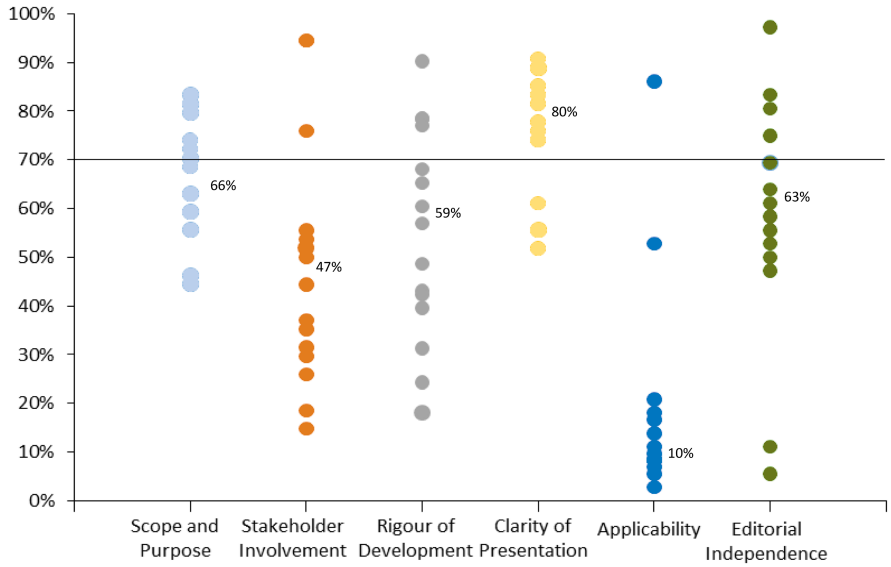

FIGURE 2 Quality assessment by AGREE II in the whole group of clinical practice guidelines on the management of status epilepticus. The score is reported by domain as a dot for each guideline and as the median score for the domain.

3.2.4 | Management of RSE/SRSE

For RSE, alternative treatments were midazolam (12 of 12 CPGs), propofol (12), barbiturate coma (11), and ketamine (2) (Table 4E). Concerning the titration endpoint for EEG monitoring during anesthetic therapy, 7 of 10 CPGs recommend burst-suppression pattern or seizure suppression as endpoints, only 1 CPG explicitly recommends using only the burst-suppression patter, whereas background suppression was suggested as titration endpoint in 4 CPGs (Table 4F).

For SRSE, only four CPGs[e11-e13,e15] reported specific recommendations. Among the alternative therapies for both RSE and SRSE, ketogenic diet (7), immunomodulating agents (6), surgery (6) and electric/magnetic stimulations (6), and hypothermia (4) were suggested (Table 4G).

3.2.5 | Specific management issues for non-motor SE

Nine of 13 CPGs reported recommendations for non-motor SE. Six CPGs recommended less aggressive treatment for NCSE than CSE, whereas one recommended the same treatment as CSE; two others provided other specific indications (Table 4H,I).

3.2.6 | Other issues

Only 6 of 16 CPGs provided some kind of tools or algorithms for helping the implementation of recommendations in clinical practice: 5 on general and treatment management[e7,e8,e11,e13,e16] and one on treatment only.[e12] Recommendations for research are provided by only two CPGs[e10,e14] concerning the most effective and safest ASM to treat established convulsive SE and convulsive RSE.

3.3 | Quality of evidence and agreement among recommendations

In the topics "pre-hospital management of early SE" and "hospital pharmacological treatment of early SE" (Table 3), most CPGs reported a high quality of evidence. Indeed, there was also agreement about the first recommended drugs (midazolam and lorazepam). In the topic "hospital pharmacological treatment of established SE," the disagreement on the level of quality of evidence among CPGs seems to reflect the different recommended drugs. In the case of all other topics (Table 3), recommendations are without level of quality of evidence, or based on expert opinion, and almost all these topics showed disagreement or fragmentation of recommendations. Two exceptions were the value of the EEG as diagnostic tool and the first recommended drug treatment for RSE, although the basis of the recommendations was expert opinion.

4 | DISCUSSION

In recent years, several health authorities and professional organizations with wide international or national audience have been involved in the development of CPGs for the management of SE. Our systematic review disclosed that these documents were flawed by several methodological issues. Confirming our hypothesis, the "Applicability" domain was particularly neglected, but also "Stakeholder Involvement" and "Rigor of Development" were overlooked. Other major findings

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TABLE 2 Quality appraisal by AGREE II domain scores for each individual clinical practice guideline.

Developer/year	Scope and purpose (%)	Stakeholder involvement (%)	Rigor of development (%)	Clarity of presentation (%)	Applicability (%)	Editorial Independence (%)
EFNS 2010[e1]	59	19	40	56	3	64
NCCS 2012[e2]	63	26	68	81	8	6
SNA 2013[e3]	44	15	31	52	8	58
ESICM 2013[e4]	80	35	60	74	10	50
ACEP 2014[e5]	72	52	78	78	7	75
ACNS 2015[e6]	69	37	18	61	8	53
AES 2016[e7]	83	56	78	85	14	69
SEN 2016[e8]	59	54	43	89	21	47
EMSAC 2017[e9]	74	30	49	74	17	61
SIGN 2018[e10]	81	94	77	91	53	81
JSN 2018[e16]	63	57	75	81	21	89
ACN 2019[e11]	46	31	24	56	8	69
LICE 2020[e12]	56	44	57	76	6	56
SRLF/SFMU 2020[e13]	63	50	42	89	11	11
NICE 2012/2022[e14]	81	94	90	83	86	83
DGN/OGN 2021[e15]	70	76	65	83	18	97

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TABLE 3 Topics covered by recommendations according to declared scope of each clinical practice guideline, agreement among recommendations and evidence supporting recommendations.

Phase	Topic coverage (*N*)	Agreement between CPGs on first recommended intervention (% of CPGs)		Evidence supporting the recommendations (% of CPGs)
Pre-hospital early SE general management	8	100% = protect airway/support breathing 62.5% = IV access; ECG/cardiorespiratory monitoring 50% = blood glucose 25% = seizure onset time; self-protection		100% = No grading or expert opinion
Pre-hospital early SE pharmacological treatment	11	100% = MDZ 63% = DZP	54% = LZP 27% = CLO	67% = High/intermediate QoE 33% = High QoE
Hospital SE general management	12	83% = lab tests 67% = ECG; protect airway/support breathing/intubation	36% = IV access 27% = Neurological exam 9% = seizure time onset; imaging; blood glucose	100% = No grading or expert opinion
Hospital SE aetiologic diagnosis	11	82% = imaging 64% = lab tests; lumbar puncture 33% = neurological exam 27% = autoimmune profile		100% = No grading or expert opinion
Hospital SE diagnostic EEG	11	100% = Indication for suspected NCSE *Type*: 73% = continuous EEG 27% = no indication	*Timing*: 27% = within 60–90 min 18% = "asap" 9% = within 24 h 36% = no indication/other	73% = No grading or expert opinion 18% = intermediate/low QoE 9% = high QoE
Hospital pharmacological treatment - 1st line	12	100% = LZP 67% = DZP; MDZ 25% = CLO 8% = DZP + PHT		50% = high QoE 33% = No grading 8% = intermediate QoE 8% = low QoE
Hospital pharmacological treatment - 2nd line	13	62% = VPA 62% = PHT 46% = fosPHT	38% = PB; LEV 15% = LZP; DZP + PHT 8% = LCS; MDZ	38% = high QoE 31% = intermediate QoE 31% = No grading
Hospital pharmacological treatment - 3rd line (RSE)	12	100% = MDZ; PROP 92% = BARB 17% = KET		67% = No grading or expert opinion 17% = Low QoE 8% = High QoE 9% = intermediate QoE
Hospital pharmacological treatment - 4th line (SRSE)	4	50% = same of 3rd line 50% = other drugs then of 3rd line		100% = No grading or expert opinion

(Continues)

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TABLE 3 (Continued)

Phase	Topic coverage (*N*)	Agreement between CPGs on first recommended intervention (% of CPGs)	Evidence supporting the recommendations (% of CPGs)
SE EEG monitoring	10	90% = burst suppression 70% = seizure suppression 40% = background suppression	90% = No grading or expert opinion 10% = low QoE
NCSE treatment	9	89% = specific indications 11% = same treatment as CSE	89% = No grading or expert opinion 11% = low QoE

Abbreviations: CLO, clonazepam; CPG, clinical practice guidelines; CSE, convulsive status epilepticus; DZP, diazepam; fosPHT, fosphenytoin; IV, intra-venous; LCS, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; NCSE, non-convulsive status epilepticus; PB, phenobarbital; PHT, phenytoin; PROP, propofol; QoE, quality of evidence; RSE, refractory status epilepticus; SE, status epilepticus; SRSE, super-refractory status epilepticus; VPA, valproic acid.

regard commonalities and discrepancies in recommendations. Neglected aspects were the development of implementation tools and the recommendations for research.

The gap between the management of SE based on CPGs and actual clinical practice consistently reported over the decades[6-11] may be partly due to the inherent limitations of the CPGs produced so far.

4.1 | Domains of quality of CPGs on status epilepticus

The domain of "Applicability", as measured by the AGREE II,[16] includes four items related to planning, undertaking, and evaluating implementation: (1) facilitators and barriers of guideline implementation, (2) resource considerations, (3) monitoring or audit criteria, and (4) implementation tools (instructions, summary documents, check-lists, algorithms). Guidelines featuring implementation instructions or tools are more likely to be used and in some cases also have impact on clinical outcomes.[19] Decision-support tools (reminders, educational materials), feedback, and audit procedures improve provider adherence to guidelines and can also improve clinical outcomes.[29-31] Three systematic metareviews[17-19] on CPG quality show consistently that "Applicability" scores the lowest among other domains (mean scores range 22%–44%). A systematic review of CPGs in the field of epilepsy shows an "Applicability" mean score of ~30%.[24] The authors expressed particular concern about this result and suggested that the lack of applicability may be one of the main reasons for the limited adoption of CPGs on epilepsy in clinical practice.

In the specific case of SE, we showed a particularly low mean score (18%) of the "Applicability" domain. This fact could be explained by different factors. SE is a heterogeneous condition that results and often represents the endpoint of many neurological or systemic disorders and thus the definition of indicators and implementation tools could be particularly difficult. Another relevant factor could be associated with the domain with the second-lowest score, "Stakeholder Involvement" (47%). This finding is even more relevant when considering the diagnosis and treatment pathway of the patient with SE who encounters multiple professional figures in his or her journey, and who must interface at different times in the pathway and according to the complexity of the individual case. This domain is of fundamental importance to identify the network of interested health professionals and the definition of the actual clinical issues to be coped with along the entire pathway management of SE, and thus important

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TABLE 4 Synthesis of the recommendations on status epilepticus reported in the 16 clinical practice guidelines included.

4 (A) Pre-hospital management of early status epilepticus:		**12 CPGs**
Target condition 6 CPGs	Type of SE specified:	
	Indications only for CSE:	5 [e1,e7,e8,e10,e14]
	Indications for CSE and other forms:	1 [e13]
Target health professional 3 CPGs	Trained paramedics:	1 [7]
	Persons close to the patient and health personnel:	1 [e8]
	Trained clinical personnel, family members/ carers with appropriate training:	1 [e14]
General management 8 CPGs	Protecting the airway and supporting breathing:	8 [e7–e10,e12–e15]
	Establishing IV access:	5 [e7–e10,e14]
	ECG monitoring/cardiorespiratory:	5 [e7,e10,e13-e15]
	Measuring blood glucose:	4 [e7–e9,e13]
	(in case of hypoglycemia, administering glucose and thiamine)	3[e7,e8,e13]
	Reporting the seizure onset time:	2 [e7,e8]
	Following the person's individualized emergency management plan, if available:	1 [e14]
General management timing 4 CPGs	In the first 0–5 min:	2 [e7,e11]
	In the first 0–10 mins:	1 [e14]
	As soon as possible:	1 [e10]
	Do not specify any time deadline:	8 [e1,e3,e5,e8,e9,e12,e13,e15]
Pre-hospital drug treatment 11 CPGs	As first choice or equivalent to other drugs:	
	MDZ (8 IM, 7 BUC, 6 IN, 1 REC, 1 IV):	11 [e1,e3,e7-e15]
	DZP (5 IV, 2 REC):	7 [e1,e3,e7,e8,e11,e12,e15]
	LZP (IV):	6 [e1,e3,e8,e11,e13,e15]
	CLO (IV):	3 [e11,e13,e15]
	As second choice:	
	LZP (IV):	3 [e9,e10,e14]
	DZP (IV):	2 [e10,e14]
	Negative recommendation:	
	DZP:	1 [e9]
4 (B) Hospital general management of status epilepticus:		**13 CPGs**
Target health professional 2 CPGs	Treatment team (including a physician and nurse):	1 [e2]
	Anesthetists and neurologist:	1 [e14]
General management 12 CPGs	Specific laboratory tests:	10 [e1–e3,e7,e10–e12,e14-e16]
	All suggest dosage of ASMs levels, study of hepatic and renal function. One suggests check convulsion-inducing drugs (including theophylline)	
	Protecting the airway and supporting breathing:	6 [e1–e3,e7,e8,e12,e16]
	Intubation:	5 [e2,e3,e13,e15,e16]
	Reporting the seizure onset time:	1 [e7]
	Different indications depending on the type of SE (including NCSE):	2 [e10,e13]
	Using an in-house protocol for general management/pharmacological treatment:	1 [e1]
	Intervention in ICU recommended:	
	Early SE:	1 [e14]
	Established SE:	2 [e3,e13]
	RSE stage:	8 [e1,e2,e8,e10-e13,e15]
	Following the person's individualized emergency management plan, if available:	1 [e14]

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TABLE 4 (Continued)

4 (B) Hospital general management of status epilepticus:		**13 CPGs**
Timing of general management 6 CPGs	*As soon as possible*:	1 [e3]
	0-5 min:	1 [e7]
	Subdivision indications into 2 stages (immediate 0-15 min and urgent 0-60 min):	1 [e2]
	Subdivision indications into 3 stages (<30, <60, >60 min):	2 [e14,e16]
	Regular monitoring (initially at least daily):	1 [e15]
Type of etiologic investigation 11 CPGs	Diagnostic imaging (2 CT, 5 CT/MRI, 2 do not specify further):	9 [e2,e3,e8,e11-e16]
	Specific laboratory tests: (almost all of them suggest using toxicology panels)	5 [e2,e5,e8,e13,e14]
	Lumbar puncture:	6 [e2,e8,e12-e14,e16]
	Neurologic exam	3 [e8,e11,e13]
	Specific guidance for "de novo" SE:	2 [e8,e13]
	Investigate autoimmune etiology:	3 [e2,e13,e16]
	Guidance on differential diagnosis:	2 [e13,e14]
	Searching for etiology without specific indications:	2 [e1,e10]
Timing of etiologic investigation 4 CPGs	*As soon as possible*:	3 [e2,e12,e13]
	Simultaneously with ASMs treatment:	1 [e5]
4 (C) EEG as diagnostic tool:		**12 CPGs**
Indication 11 CPGs	If suspected NCSE:	11 [e3,e4,e6,e8,e10-e16]
	To confirm/exclude psychogenic status:	2 [e15,e16]
Timing 7 CPGs	As soon as possible:	2 [e6,e13]
	Simultaneously with ASMs treatment	1 [e16]
	60-90 min:	3 [e4,e11,e12]
	24 h: (*unavailability of the EEG should not discourage/delay treatment*)	1 [e10]
Type of monitoring and other details 9 CPGs	EEG prolonged or continuous:	8 [e3,e4,e6,e8,e11,e13,e15,e16]
	Video EEG: (1 [e11] suggests sending the patient to a hospital where video EEG is available)	4 [e3,e4,e6,e8,e11]
	Minimum duration 24–48 h:	3 [e2,e6,e13]
	More than 48 h: (comatose/pharmacologically sedated patients, periodic discharges)	2 [e2,e6]
	Frequency of review and interpretation about every 12 h:	1 [e6]
	Small (4–9) number of leads if complete recording is not available:	1 [e13]
4 (D) Hospital pharmacological treatment of early and established status epilepticus:		**13 CPGs**
Timing 13 CPGs	Provide time indications for the first line of treatment:	13 [e1–e3,e5,e7,e8,e10–e16]
	Subsequent treatments:	
	Based on both, temporal criteria and treatment failure:	7 [e3,e8,e11–e14,e16]
	Based on previous medication failure, without time indications:	4 [e1,e2,e5,e15]
	Based on temporal criteria (5-20–40 min; 5-30–60 min):	2 [e7,e10]

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TABLE 4 (Continued)

4 (D) Hospital pharmacological treatment of early and established status epilepticus:					**13 CPGs**
First line 12 CPGs	First choice:			Second choice:	
	LZP IV:	12 [e1–e3,e7,e8,e10–e16]		DZP REC:	6 [e2,e7,e12,e14-e16]
	MDZ IM:	4 [e2,e7,e11,e12]		MDZ BUC:	5 [e7,e12,e14-e16]
	MDZ IV:	3 [e12,e15,e16]		MDZ IM:	4 [e2,e13,e15,e16]
	MDZ buc/IN:	1 [e10]		MDZ IN:	3 [e7,e12,e16]
	DZP IV:	8 [e1,e7,e8,e10,e11,e12,e15 e16]		PB IV:	2 [e7,e12]
	DZP+PHT:	1 [e3]		PHT/fosPHT, VPA, LEV:	1 [e2]
	CLO IV:	3 [e11,e13,e,15]			
	IV as the best route of administration:				5 [e2,e12–e15]
	Repeat doses of BZD (after 5-20 min) if there is no response: (5 [e7,e11–e14] excluded MDZ)				8 [e7,e10–e16]
	Medications IV in loading doses if the patient has not been taking usual medication adequately:				1 [e10]
	Use an adequate single full dose rather than multiple smaller doses:				1 [e7]
	Refer to specific types of SE (NCSE or other forms: see Table 4H,I):				3 [e1,e10,e14]
Second line: 13 CPGs	First choice:			Second choice:	
	VPA:	8 [e2,e5,e7,e10,e11,e13-e15]		LEV:	6 [e2,e3,e5,e7,e8,e12]
	PHT:	8 [e2,e5,e8,e10-e12,e14,e16]		PB:	5 [e2,e3,e5,e7,e15]
	fosPHT:	6 [e2,e5,e13-e16]		VPA:	3 [e3,e8,e12]
	DZP+PHT:	2 [e1,e3]		LCS:	3 [e2,e8,e12]
	PB:	5 [e8,e11–e13,e16]		PHT:	2 [e7,e15]
	LEV:	5 [e11,e13-e16]		fosPHT:	1 [e7]
	LZP:	2 [e1,e3]		TPM:	1 [e11]
	MDZ (continuous):	1 [e16]		PROP (continuous):	1 [e5]
	LCS:	1 [e11]			
	Medications IV in loading doses if the patient has not been taking usual medication adequately:				3 [e2,e8,e11]
	Refer to specific types of SE (NCSE or other forms: see Table 4H,I):				5 [e1,e8,e11,e13,e14]
4 (E) Management of RSE/SRSE:					**12 CPGs**
Third line (RSE): 12 CPGs	Continuous anesthetic therapy				
	First choice			Second choice	
	MDZ/PROP: (2 [e13,e,15] also in combination)	12 [e1–e3,e7,e8,e10–e16]		Ketamine:	3 [e2,e3,e13]
	Barbiturate coma:	11 [e1–e3,e7,e8,e10–e12,e14–e16]		Inhalation anesthetics:	2 [e2,e3]
	Ketamine:	2 [e11,e12]		Alternative ASMs: (CBZ, TPM, CLO)	2 [e2,e3]
	Refer of specialist advice in case of RSE or NCSE/SRSE:				2 [e10,e13]
	Repeat second-line therapy or start anesthetic therapy depending on the etiology or severity of the seizure:				5 [e1,e7,e13,e15,e16]
	Specify that previously used ASMs should be maintained:				2 [e8,e12]
	Consider also palliative treatment:				1 [e15]
	Consider the patient's will and the existence of an advance directive:				1 [e15]

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TABLE 4 (Continued)

4 (E) Management of RSE/SRSE:		**12 CPGs**
Fourth line (SRSE) 5 CPGs	Switching to a different anesthetic or combination with a second agent:	1 [e12]
	Use of alternative ASMs (like TPM or PRP) and anesthetics (e.g. inhalant anesthetics):	1 [e15]
	Use the same treatment of third line:	3 [e11,e13,e16]
4 (F) EEG monitoring during anesthetic therapy:		**10 CPGs**
EEG monitoring during anesthetic therapy 10 CPGs	Titration endpoints:	
	Background suppression:	4 [e2,e6,e12,e15]
	Burst-suppression:	9 [e1–e3,e6,e11–e15]
	Specific for PROP/barbiturate:	2 [e1,e3]
	Seizure-suppression:	7 [e1-e3,e6,e13-e15]
	Specific for MDZ:	2 [e1,e3]
	Duration of endpoint maintenance:	
	For 4 h:	1 [e3]
	For 12–24 h:	2 [e8-e14]
	For at least 24 or 24–48 h	5 [e1,e2,e11–e13]
	Tapering modality	
	Reduce gradually anesthetics over approximately 6 h under EEG control:	1 [e13]
	Infusion rate every 1–2 h, adapting the rate to electroclinical condition:	1 [e12]
	If tapering fails continue anesthesia, with or without the addition of another agent:	4 [e2,e3,e12,e13]
	Increase the duration of the following anesthesia cycle:	2 [e2,e12]
4 (G) Alternative therapies for specific cases of RSE-SRSE:		**7 CPGs**
Pharmacological 6 CPGs	Immunomodulating therapies (corticosteroids, IVIG, PEX):	6 [e2,e3,e8,e11–e13]
	(cyclophosphamide and rituximab in selected cases)	1 [e12]
	Magnesium:	3 [e3,e8,e12]
	Other therapies (e.g. calcium channel blockers):	2 [e3,e12]
Non-pharmacological 7 CPGs	Ketogenic diet:	7 [e2,e3,e8,e11–e13,e15]
	Surgery:	6 [e2,e3,e8,e11,e12,e15]
	Vagus nerve stimulation:	6 [e2,e3,e8,e11,e12,e15]
	Electroconvulsive therapy:	5 [e2,e3,e8,e12,e15]
	Hypothermia:	4 [e2,e3,e8,e12]
	Transcranial magnetic stimulation:	3 [e2,e3,e12]
	Deep brain stimulation:	2 [e3,e12]
	Trigeminal nerve stimulation:	1 [e12]
	In case of paraneoplastic syndrome, rapid and aggressive treatment of the primary neoplasm:	1 [e12]
	Recommendation against the use of allopregnanolone and systemic hypothermia:	1 [e15]
4 (H) NCSE:		**12 CPGs**
EEG 10 CPGs	EEG in diagnostic phase:	10 [e3,e4,e6,e8,e10–e14,e16]
	Specified clinical conditions under which to suspect it:	3 [e4,e6,e13]

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TABLE 4 (Continued)

4 (H) NCSE:		**12 CPGs**
Treatment 9 CPGs	BZDs as first-line treatment:	3 [e10,e14,e16]
	Maintain or reinstate the usual oral ASMs therapy:	2 [e10,e14]
	Give priority to the treatment of SE cause (which determines the prognosis):	1 [e8]
	With respect to the treatment of convulsive SE	
	Less aggressive (treatment is less urgent, drugs administration can be slowed down and the dosage modulated, non-sedative ASMs should be added, consider first side effects and complications, anesthetic therapy is not mandatory):	6 [e8,e12–e16]
	Same treatment	1 [e3]
Specific forms 6 CPGs	NCSE "with confusional symptoms":	
	BZDs as first-line treatment:	1 [e8]
	ASMs as second-line treatment:	1 [e13]
	"Absence SE": *use BZDs, reintroduce usual ASMs therapy and, if symptoms persist, use VPA IV*:	1 [e13]
	"Absence SE" and "Myoclonic SE": *don't use PHT*	1 [e16]
	"Subtle SE": use the same treatment of refractory CSE:	2 [e1,e8]
	Refractory NCSE stage:	
	Sequential use of different ASMs:	2 [e8,e12]
	Aggressive treatment not recommended/reserved for situations in which the ongoing SE is a higher risk than the treatment itself:	4 [e8,e12,e13,e15]
4 (I) Other forms than NCSE:		**2 CPGs**
Other forms than NCSE	Modulating therapy according to the characteristics of the patient and SE (focal motor, myoclonic, tonic seizures):	1 [e13]
	IV therapy: fosPHT, VPA, LEV, LCS, PB; the rate of administration of the drugs slowed down and the dosage modulated according to the terrain and the semiology of the seizures	
	Alternative, oral therapy with CBZ, PHT, PRP, ZNS, TPM, pregabalin, PB	
	In case of RSE, anesthetic treatment for situations in which the ongoing SE is a higher risk than the treatment itself	
	BZDs for SE with myoclonic seizures without perceptible disturbances of consciousness (in idiopathic generalized epilepsy):	1 [e13]
	General anaesthetic not indicated in continuous partial epilepsy:	1 [e13]
	"Complex partial" SE: first- and second-line treatment as for CSEs, in case of failure try more ASMs (PB, VPA, LEV) before general anesthesia (if necessary, apply the same protocol of refractory CSE):	1 [e1]

Abbreviations: ASM, anti-seizure medication; BUC, buccal; BZD, benzodiazepine; CLO, clonazepam; CPG, clinical practice guidelines; CSE, convulsive status epilepticus; DZP, diazepam; fosPHT, fosphenytoin; IM, intra-muscolar; IN, intra-nasal; IV, intra-venous; IVIG, intra-venous immunoglobulin; LCS, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; NCSE, non-convulsive status epilepticus; PB, phenobarbital; PEX, plasma exchange; PHT, phenytoin; PROP, propofol; PRP, perampanel; REC, rectal; RSE, refractory status epilepticus; SE, status epilepticus; SRSE, super-refractory status epilepticus; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

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for the implementation of recommendations. Indeed, in the field of SE, most developers were professional organizations of neurologists, anesthesiologists, or emergency medicine physicians, with little or no involvement of other health professionals (nurses, neurophysiology technicians, internal medicine physicians, decision makers) or patient representatives. Finally, also the domain "Rigor of Development" was particularly problematic in CPGs, both in terms of reliability of terminology and in terms of evaluating and ranking the evidence underlying the recommendations.

4.2 | Recommendation issues that could impact the applicability of CPGs

4.2.1 | Time of seizure onset

Most CPGs did not recommend reporting the time of seizure onset, or at least an estimate considering the last time the patient was seen to be well. This point is of particular importance, also considering the current SE operational definition that considers status as a time-dependent emergency.[1,32] The duration of SE before diagnosis and first treatment should be something worthy of standardization and recommendation in the development of new CPGs. The spin-offs can be multiple: from faster treatment delivery to future stratification of outcomes in relation to the timing of interventions linked to the presumed time of seizure onset.

4.2.2 | Targeted protocols for SE with out-of-hospital or in-hospital onset

Only one CPG emphasized the importance of establishing and using in-hospital management and treatment protocols, and no CPG provides specific indications for the management of SE with in-hospital onset. The shared conclusion of the studies conducted to date on this topic[11,33,34] is that a worse prognosis in-hospital SE cases should be related to the more severe etiologies. A greater consideration of the site of onset, combined with early identification and treatment of modifiable risk factors, could positively influence the outcome of these patients.

4.2.3 | Diagnostic procedures

EEG confirms itself as the examination most recommended; however, not all of the CPGs provided time indicators for its execution. This consideration should be underscored in light of the increasing recognition of NCSE with the availability of long-term EEG monitoring.[4] In these cases, an early diagnosis is associated with a timely intervention. A further point that belongs to the domain of applicability was the absence in all CPGs of clinical (and/or EEG) criteria to define response to pharmacological treatments. Although the definition of seizure cessation (and thus response) is evident in CSE it is not so for NCSE. This issue obviously poses major organizational challenges as it implies increased use of EEG and resources (technicians, neurophysiologists).

4.2.4 | General management and treatment of SE

Most CPGs did not provide any time indications regarding the application of general management activities and only three specified to whom these indications are addressed. Pharmacological treatment of early SE showed a substantial agreement among CPGs, probably due to the good level of evidence on the basis of recommendations. Instead, the switch from one line of therapy to the next in case of failure was decreed variably, either by time criteria (two CPGs) or by criteria of failure of the previous line (four), and sometimes by a dual indication (seven).

The use of ASMs was predominantly suggested as a second line of therapy, but some disagreement has been observed on which ASM to recommend. This is probably because the recent CPGs also include new ASMs that were not considered by the older CPGs because they were not yet in use at the time of their development.

Midazolam, propofol, or barbiturates were concordantly recommended as alternative choices for RSE, despite the scarcity of evidence. Recommendations usually did not provide a specific and easily enforceable indication, leaving ample room for the clinician to act the modulation depending on the severity of the picture, the etiology, and personal experience.

The majority of CPGs provided indications on EEG monitoring during anesthetic therapy in RSE: in most cases, the recommended endpoint is seizure suppression or burst-suppression, with no indication of superiority of one or the other. Regarding the timing of endpoint maintenance, there is a wide variability (from 4 h to >24 h). The mode of tapering is indicated in only two CPGs, leaving ample room for individual decision.

Regarding the issue of the ethical aspects of prolonged treatment of resistant forms, only one CPG[e15] suggests the possibility of initiating palliative therapy, although it does not provide any further specific indications, emphasizing the importance of considering the patient's wishes. It is currently not possible to indicate a time limit beyond which intensive treatment should be considered.

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4.3 | Limitations

Our systematic review—the first to assess the methodological and content characteristics of CPGs on SE in adults—also has some limitations.

Our search strategy had flaws in finding CPGs from non-Western countries. In fact, one CPG from Japan was not found by the strategy but flagged by an expert in the field during the peer-review process. The literature search on CPGs is particularly challenging because of the nature of the documents, which in many cases are "gray literature" without publication in peer-reviewed journals. Methodologically, any literature search will always have limitations because it is the result of a trade-off between precision and sensitivity. However, to compare with our results, the systematic review of CPGs on any aspect of epilepsy conducted by the International League Against Epilepsy (ILAE) Guidelines Task Force[24] retrieved only three CPGs from Asia/Oceania and one from Africa, of the 63 retrieved.

Another limitation concerns the process of extracting guideline metadata (title, year, developer, country of origin, topic/scope, development method/quality rating system), which was performed by only one researcher. However, all other procedures (literature sifting, extraction of data on recommendations, quality assessment, data synthesis) were performed by at least two researchers.

From a methodological viewpoint, we used an unvalidated method to compare the certainty of the evidence methods underlying the recommendations.

Finally, our results are limited to adults only, due to the exclusion of the child population from our scope. In this age group, however, SE has a particular etiology and prognosis.

5 | CONCLUSIONS

The result of this systematic review highlights the following suggestions for future CPGs on SE:

1. All health care stakeholders involved in the management of SE should be included in the task force developing a CPG;
2. Recommendations should be developed following well-established methodological tools (e.g. GRADE[35]);
3. CPGs should provide organizational recommendations, considering the setting, time, and details of interventions in most important aspects of SE management;
4. Decision-support tools and indicators for auditing implementation should be provided;
5. Research aims should be prioritized. Gray areas for future research are (1) the development of a shared framework model for the management of SE; (2) the organizational aspects to speed up the management of SE, detailing the prognostic role of settings, general procedures, diagnosis and support; (3) the milestones to decide the changes from pharmacological treatment to another in the different phases of SE; and (4) management of the NCSE.
6. Ethical aspects for management of people in the terminal phase of an incurable disease (e.g., brain neoplasms) should be discussed.

AUTHOR CONTRIBUTIONS

Conceptualization: Luca Vignatelli, Stefano Meletti, Giada Giovannini, Elena Pasini, Roberto Michelucci, Francesca Bisulli, Paolo Tinuper, and Lidia Di Vito. Methodology: Luca Vignatelli and Maria Camerlingo. Software: Stefania Mazzoni. Data curation: Valentina Tontini and Stefad nia Mazzoni. Investigation: Luca Vignatelli, Valentina Tontini, Maria Camerlingo, Stefania Mazzoni, and Lidia Di Vito. Validation: Luca Vignatelli and Lidia Di Vito. Formal analysis: Luca Vignatelli, Valentina Tontini, Stefania Mazzoni, and Lidia Di Vito. Supervision: Luca Vignatelli and Paolo Tinuper. Funding acquisition: Roberto Michelucci, Francesca Bisulli, and Paolo Tinuper. Project administration: Luca Vignatelli. Writing - original draft: Luca Vignatelli, Valentina Tontini, Stefano Meletti, and Lidia Di Vito. Writing - review & editing: Maria Camerlingo, Giada Giovannini, Elena Pasini, Roberto Michelucci, Francesca Bisulli, and Paolo Tinuper.

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CONFLICT OF INTEREST STATEMENT

All authors have completed the International Committee of Medical Journal Editors (ICMJE) Form for Disclosure of Potential Conflicts of Interest. P.T. is the co-author of two of the evaluated guidelines. This author did not assess the quality of these documents and did not pass judgment on them. S.M. and R.M. are co-authors of one of the evaluated guidelines. These authors did not assess the quality of this document and did not pass judgment on it. L.D.V. received support for attending meetings from Angelini Pharma. F.B. received consulting fees from Angelini

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Pharma and Eisai. R.M. received honoraria for lectures from Eisai and received support for attending meetings from Angelini Pharma and Eisai. S.M. received honoraria for lectures from UCB Pharma, Eisai, and Jazz pharmaceuticals, and received support for attending meetings from UCB Pharma and Eisai. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

DATA AVAILABLITY STATEMENT

The data supporting the findings of this study are provided in tables in the main text, in supplementary materials, and in a public data repository (10.5281/zenodo.6363324 and 10.5281/zenodo.10548430).

ROLE OF THE SPONSORS

The funding body had no role in the design of this study or any role during its execution, analyses, interpretation of the data, or decision to submit results.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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