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SPECIAL ISSUE ARTICLE

Recognizing seizure clusters in the community: The path to uniformity and individualization in nomenclature and definition

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Abstract

Seizure emergencies experienced by patients with epilepsy include status epilepticus and seizure clusters. Although an accepted definition of status epilepticus exists, no clear consensus definition of seizure clusters has emerged; this is further complicated by the appearance in the literature of various empirically based definitions that have been developed for clinical trial study designs. In general, patients with intractable epilepsy have been shown to have a significant risk for acute episodes of increased seizure activity called seizure clusters (also referred to as acute repetitive seizures, among other terms) that differ from their usual seizure pattern. Duration (e.g., number of hours or days) is often included in the definition of a seizure cluster; however, the duration may vary among patients, with some seizure clusters lasting ≥24 h and requiring long-acting treatment for this period. In addition to seizure cluster duration, the time between seizures and possible acceleration in seizure frequency during the cluster may be important variables. The recognition and treatment of seizure clusters require urgent action because episodes that are not quickly and appropriately treated may lead to injury or progress to status epilepticus or potentially death. Most seizure clusters occur outside a medical facility (in the community) and treatment is usually administered by nonmedical individuals; therefore, health care providers may benefit from a clear description of these potential seizure emergencies that they can then use to educate patients and caregivers on the prompt and appropriate identification of seizure clusters and administration of rescue therapy. Here we explore why greater uniformity is needed in the discussion of seizure clusters. This exploration examines epidemiologic studies of seizure clusters and status epilepticus, inconsistencies in nomenclature and definitions for seizure clusters, practical application of seizure cluster terminology, and the potential use of acute seizure action plans and patient-specific individualized definitions in the clinical setting.

KEYWORDS

acute repetitive seizure, epilepsy, prolonged acute convulsive seizure, rescue, status epilepticus

1 | INTRODUCTION

Epilepsy can be described as a spectrum disorder with interpatient variability of such characteristics as seizure type, frequency, and severity.[1] For some patients, seizures may follow a nonrandom, patient-specific pattern.[2,3] However, seizure clusters and even status epilepticus may transpire as acute occurrences outside the patient's usual pattern and necessitate prompt identification and treatment, which can be outlined in a written action plan.

Although status epilepticus has an accepted definition put forth by the International League Against Epilepsy (ILAE), this is not the case for seizure clusters.[4,5] No consensus definition has been agreed on for this term in the literature or among health care providers (HCPs), patients, and caregivers.[6,7] In the clinical environment, this may lead to a gap in communication between the HCP and the patient and caregiver regarding how seizure clusters should be identified.[8] In addition, the use of a variety of terms to label these potential seizure emergencies may lead to confusion for patients and caregivers.[6,8]

Differences in nomenclature and definitions for seizure clusters may be influenced by the participation of multiple contributors to the care of patients with epilepsy, including caregivers, primary care physicians, specialists, nurses, and pharmacists.[6] In the clinical setting, this lack of standardization among stakeholders can be a problem for both the HCP and the patient and caregiver, potentially leading to suboptimal use of rescue therapy.[6,8]

Uniformity and consistency in the terminology for discussing seizure clusters among all stakeholders involved in the care of the patient is needed.[4,6] In addition, the definition used in clinical practice should be sufficiently flexible to address patients' individual differences in seizure frequency and cluster variation,[7] with components including time between seizures, number of seizures, risk of injury, differentiation from the patient's usual seizures, and patient and caregiver experience or perception of the seizures.

2 | EPIDEMIOLOGY

The prevalence of epilepsy is ~50 million people worldwide, with 5 million receiving a diagnosis of epilepsy each year.[9] In Europe, the prevalence has been estimated as 2.6 to 6 million people.[10] According to the US Centers for Disease Control and Prevention, the prevalence of patients with active epilepsy is ~3.5 million people in the US population (3 million adults and 470 000 children).[11] Patients with intractable epilepsy appear to be at higher risk for seizure clusters.[12] Some studies have estimated that ~30%–40% of patients with epilepsy are drug resistant.[13]

Key Points

- There is no agreed-on nomenclature or definition for seizure clusters (unlike status epilepticus) in the literature or clinical setting
- Inconsistency of terms can lead to difficulty reconciling data across epidemiologic studies of populations with seizure clusters
- Use of different terms by clinicians, patients, and caregivers may lead to communication gaps and potential treatment overuse or underuse
- Practical application of seizure cluster terminology further demonstrates current inconsistencies in nomenclature and definitions
- A clear definition of, and further research on, seizure clusters may help identify and treat this condition

Drugs for managing acute repetitive seizures have been given orphan designation by the US Food and Drug Administration (FDA), indicating treatment for a rare condition affecting fewer than 200 000 persons in the United States.[14,15] In published studies, the prevalence of seizure clusters has been shown to vary widely, from 13% to 76% in outpatient studies of patients with epilepsy and from 18% to 61% in inpatient studies of patients with epilepsy, with different definitions for seizure clusters used among the studies.[4] In a US database study of outpatient adults, seizure clusters were defined as ≥3 seizures in a 24-h period (or three times the daily average), and seizure clusters had been reported for 612 of 4116 patients (14.9%).[16] Another study of inpatient and outpatient adults that defined seizure clusters as ≥3 seizures in 24 h found a 29% (41/141) prevalence of seizure clustering.[17] A UK study of the General Practice Research Database found the prevalence of individuals at risk for acute repetitive seizures in the general population to be 2.3/10 000, with the higher rates in the youngest age groups and decreasing with age through older patient groups.[18] In addition, some epilepsy syndromes are characterized by seizure clusters; for example, seizure clusters are the hallmark clinical feature of the rare epilepsy syndrome caused by *PCDH19* gene mutation, and conventional antiseizure medicines (ASMs) are often ineffective in controlling or preventing most of these seizures.[19,20]

3 | NOMENCLATURE AND DEFINITIONS

For seizure clusters, the path to collecting epidemiologic data may be impeded by the lack of consistency in

nomenclature and definitions. Studies in the literature have proposed definitions with differing empirical characteristics, such as number of seizures and time interval involved, making it difficult to estimate an overall prevalence of seizure clusters across studies (Table 1).[8,21,22]

Additional nomenclature used for seizure clusters includes *cluster seizures; acute repetitive seizures; cyclical, serial, repetitive, crescendo*, and *recurrent seizures*; and *seizure flurries*, and may be considered a type of prolonged acute convulsive seizure in Europe.[6,8,23,24] In its consensus paper on the treatment of repetitive seizures, the Epilepsy Foundation chose to use the term *seizure cluster*.[6] The common terms seizure cluster, acute repetitive seizure, and serial seizure are not included in the ILAE classification and terminology.[25]

A published review of the medical literature and community forums examined how HCPs and the public, respectively, communicate about seizure clusters.[25] The common terms used by both HCPs and the public were *acute repetitive seizures, seizure clusters*, and *clusters*. Both the HCPs and the public mentioned frequency, duration, and timing of seizures within the cluster. However, there was a lack of consistency within and between the two groups as to what numbers for these measures were used. In addition, the definitions that HCPs used were empirically and clinically focused, whereas those from the public focused on the personal impact on patients' lives.[25]

The FDA convened an advisory panel to define seizure cluster for testing potential treatments, which resulted in a report in 1996 that provided a conceptual definition

TABLE 1 Examples of difference in nomenclature and definitions for seizure clusters in the literature

Study/review topic	Nomenclature	Definition
Rectal diazepam gel vs. placebo[26]	Acute repetitive seizures	Multiple complex partial or generalized (tonic, clonic, tonic–clonic, atypical absence, or myoclonic) seizures occurring within a 24-h period in adults or a 12-h period in children, with a pattern distinguishable from the patient's usual seizure pattern and with onset readily recognizable by a caregiver, such as a parent
Treating repetitive seizures with rectal diazepam[44]	Acute repetitive seizures	A predictable component of a patient's seizure disorder historically distinct from the patient's other epileptic seizures in type, frequency, severity, or duration and with an onset easily recognized by family and physician
Association between seizure clustering and status epilepticus[45]	Seizure clustering	≥3 seizures within a 24-h period
Prevalence of acute repetitive seizures[18]	Acute repetitive seizures	≥3 partial or generalized seizure episodes over a 24-h period
Video-electroencephalography monitoring[46]	Seizure clusters	≥3 or more complex partial seizures or generalized tonic–clonic seizures in a 4- or 24-h period
Seizure frequency in progesterone-treated women[47]	Perimenstrual seizure exacerbation	3-fold or greater level of perimenstrual (days −3 to +3) seizure exacerbation
Epilepsy diary to characterize repetitive seizures[22]	Seizure clusters	≥2 seizures in a midnight-to-midnight calendar day
Seizure clusters in drug-resistant focal epilepsy[40]	Seizure clusters	≥2 seizures occurring within 2 days in a habitual pattern that was also distinguishable from more sporadic usual seizures
Burden of seizures on patients and caregivers[27]	Seizure clusters	≥2 seizures in 24 h outside a patient's typical seizure pattern
Safety and efficacy of midazolam nasal spray[48]	Seizure clusters	≥2 seizures (focal or generalized) that lasted ≥10 min and had an observable, stereotyped, and recognizably different pattern from patients' noncluster seizure activity, with another seizure occurring within 6 h of cluster onset
Individualizing the definition of seizure clusters[7]	Seizure clusters	Individualized using a data-driven approach
Final results of phase 3 trial of diazepam nasal spray[36]	Seizure clusters	Intermittent increases of seizure activity
National Institute for Health and Care Excellence clinical guideline[24]	Repetitive seizures	≥3 seizures within 1 h

of the term *acute repetitive seizures*.[25] This definition had several components including being distinct from the patient's other seizures in frequency, severity, type, or duration.[25] Shortly afterward, a study of the safety and efficacy of diazepam rectal gel for acute repetitive seizures provided an operational definition of the term as an episode of focal impaired awareness seizures or generalized onset seizures occurring within a 12-h period in children and a 24-h period in adults with a distinguishable pattern from the patient's usual seizure pattern and with onset recognizable by a caregiver.[26]

A published review in 2006 noted that there was a variety of empirical definitions for seizure clusters in which the number of seizures (e.g., 2, 3, 2–4) and the time period (e.g., 4, 24, 48 h) vary, as well as more general definitions without such specific numbers.[12] A Harris poll in 2014 used the empirical definition of ≥2 seizures in 24 h outside the patient's typical seizure pattern.[27]

Statistical definitions of seizure clusters have been proposed that describe an increase in seizure frequency compared with what is expected from the patient's usual seizure pattern.[8,22] For example, an increase of 3- or 4-fold (or 3 standard deviations [SD]) in seizure frequency during a 3-day period may be considered seizure clustering.[12,22] Statistical approaches also have been used that examine whether the time distribution of seizures represents a random Poisson process; deviation from the random model can reflect a seizure cluster.[8,22] Such departures from the random model have been observed in many patients with refractory epilepsy and often in children with precipitating or trigger factors, such as fever and stress.[8,28]

A more recent study proposed an individualized statistical approach for identification of seizure clusters for the individual patient that includes baseline seizure frequency and distinguishes between seizure clusters and normal variation.[7] An algorithm was developed using data from the Seizure Tracker™ seizure diary database, and the results were compared with results from the application of rule-based empirical definitions. The authors found that classical cluster definition often led to seizures being misclassified as seizure clusters when they were seizures occurring with normal random fluctuations. The software algorithm they developed also helped identify seizure clusters for patients who have infrequent seizures (i.e., with interseizure intervals of >1 month) that otherwise might be missed using more conventional definitions. This statistical approach to identifying seizure clusters may potentially improve epilepsy treatment for individuals by aiding identification of previously unrecognized clusters and by preventing unnecessary treatments for seizures that had been considered previously to be clusters.[7]

4 | DEFINITIONS FOR PRACTICAL USE

Although not all seizure cluster episodes constitute a medical emergency, many meet clinical criteria for rescue therapy. Three rescue therapies are approved by the FDA for acute treatment of seizure clusters (currently defined for all three medications as intermittent, stereotypic episodes of frequent seizure activity [i.e., seizure clusters, acute repetitive seizures] that are distinct from a patient's usual seizure pattern): rectal diazepam (1997), intranasal midazolam (2019), and diazepam nasal spray (2020).[29–31] The indications for the three medications differ by the age range for which they are approved for use.[29–31]

Because seizure cluster, acute repetitive seizure, and serial seizure are not included in the ILAE classification and terminology, rescue medications specifically indicated for seizure clusters have not been approved outside the United States.

Diazepam rectal gel was the first rescue therapy for seizure clusters approved by the FDA. Studies of diazepam rectal gel in the late 1990s used the term *acute repetitive seizures*.[26,32] The original orphan designation of diazepam rectal gel, as well as the 2016 label, states that it is for management of selected, refractory patients with epilepsy on stable regimens of ASMs who require intermittent use of diazepam to control bouts of increased seizure activity.[33,34] In 2021, the diazepam rectal gel description of seizure cluster on the label was made consistent with that for intranasal midazolam and diazepam nasal spray.[29,31]

Approvals for the two intranasal formulations followed two decades after the approval of diazepam rectal gel. In 2019, a phase 3 trial evaluating the safety and efficacy of internasal midazolam used the term *seizure cluster*.[35] Characteristics of seizure clusters for this trial were ≥2 focal or generalized seizures, duration of ≥10 min, having a different pattern from the patients' noncluster seizures, and with another seizure occurring within 6 h of onset.[35] The majority of published analyses of diazepam nasal spray studies have used the term *seizure cluster*, with a definition of intermittent increases of seizure activity.[36]

In countries where regulatory bodies do not classify treatment specifically for seizure clusters, such as the European Union, clinical practice may guide treatment. Rescue treatment may be provided for repeated seizures of ≥3 seizures within 1 h[24,37,38] using formulations such as buccal midazolam[23] or diazepam rectal solution.[39] This lack of regulatory guidance illustrates the need for consensus on the definition of seizure clusters across countries and regions.

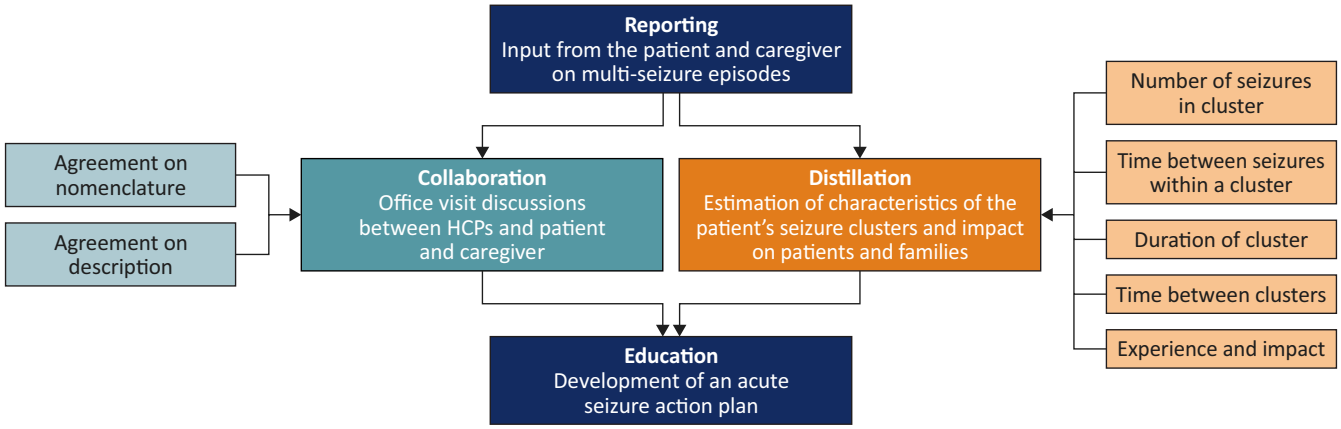

FIGURE 1 Suggested flow for defining an individual patient's seizure cluster. HCP, health care provider.

5 | CLINICAL VIGNETTES

The following clinical vignettes are provided to emphasize the differences in patients who experience seizure clusters, such as different epilepsy syndromes, age groups, and cognitive status.

Patient A is currently 17 years of age, has had drug-resistant focal epilepsy diagnosed by an epileptologist, and underwent resective brain surgery. During the follow-up to the surgery, she reports that she is not seizure-free and has experienced seizure clusters of ≥2 seizures within 2 days. These seizure clusters are distinguishable from her usual seizure pattern.[40]

Patient B is currently 9 years old with Lennox–Gastaut syndrome (LGS) and intellectual disability. During an office visit, his mother mentions that, aside from the usual pattern of brief seizures, the patient also has seizure clusters of as many as three seizures in a 2-h period.

Later that day, the father of another patient with LGS mentioned that his 19-year-old daughter, **Patient C**, has had episodes of three clusters over a period of 2 days that are distinct from her usual seizures. He remarks that the most recent cluster has had a significant negative impact on the family's day-to-day life, preventing them from leaving on a long-planned vacation.

Patient D is an 8-year-old girl with Dravet syndrome. During the previous week, she experienced an increased frequency of clonic short seizures (10–15 s in duration) that appeared during sleep and recurred every 1–1.5 h for 2–3 nights per week.

Patient E is a 10-year-old girl with epilepsy related to the *PCDH19* pathogenic variant. She was seizure-free for 2 years and then had short focal seizures (<1 min in duration) that recurred with increasing frequency from 1 seizure every 4 h to 1 seizure every 30 min during a febrile illness that occurred 8 h before presentation to the emergency department.

These vignettes demonstrate differences in the description of the cluster, including the number of seizures and duration of the episode. Because the characteristics of potential seizure clusters may vary from patient to patient,[41] it is left to the HCP to determine whether what is being described is a seizure cluster.[40] In addition, in some cases, the caregiver may not remember the number of seizures and duration of the episode, making it more difficult for the HCP to align the patient's seizure occurrence with an existing empirical seizure cluster definition.

6 | CLARITY THROUGH CUSTOMIZATION AND STANDARDIZATION

The lack of a consistent, agreed-upon definition for seizure clusters may result in a communication barrier between the HCP and the patient and caregiver that potentially could delay or prevent identification of a seizure cluster when it occurs. The use of a patient-specific acute seizure action plan (ASAP, discussed by Patel and Becker in *Introduction to Use of an Acute Seizure Action Plan for Seizure Clusters and Guidance for Implementation* in this supplement)[42] developed by the HCP in collaboration with the patient and caregiver can provide the customized guidance needed to recognize seizures that are typical and atypical for the patient and then respond appropriately.[43] The ASAP may present guidance in a tiered manner, with basic seizure safety presented as first actions; rescue medication may be required under certain circumstances; and

a call to emergency services may be reserved for specific situations. The potential benefits of an appropriate response include both stopping progression to status epilepticus and avoiding the need for transport to the hospital, and also improvements in patient safety, social function, and quality of life.[42,43]

Current definitions of seizure clusters may fail to identify seizure clusters that do not meet a prespecified threshold and may fail to account for individual variability.[7] The development of an individualized seizure cluster definition that allows for the incorporation of customized variations in the number of seizures and duration, as well as the lived experience and impact, that are specific to the patient may be helpful to enhance awareness and recognition of seizure clusters.[7] A potential process for defining the patient's seizure clusters can follow a flow that includes reporting, collaboration, distillation, and education (Figure 1).

Clear nomenclature and a consistent empirical definition are also needed for epidemiologic studies to better understand the population of patients with seizure clusters. Prospective, population-based studies that are designed with consideration of all confounding variables such as the patient's epilepsy syndrome, age, and inpatient setting may be beneficial for standardizing reports of incidence and prevalence.[21]

7 | CONCLUSION

Consistency of both nomenclature and the definition of a seizure cluster is necessary to ensure the recognition of these potential seizure emergencies and the use of appropriate treatment to stop seizure repetition and reduce the likelihood of progression to prolonged seizures or status epilepticus. Treatment can also help to prevent injury and improve quality of life. A clear understanding of what a seizure cluster entails and what action to take when one occurs can be bolstered by the availability of an acute seizure action plan with concise guidance. Individual patients and caregivers need an understanding of the patient's individual experience with seizure clusters, and the field needs consistency for accurate reporting of epidemiology and standardization of outcomes.

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Original Draft Preparation: all authors developed the initial content outline for the manuscript. Writing—Review and Editing: all authors provided critical review and revision. All authors approved the final version of this manuscript for submission to *Epilepsia*.

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CONFLICT OF INTEREST

Dr. Haut serves as a consultant for Nile AI and UCB. **Dr. Nabbout** has received consulting fees from Biogen, Eisai, Encoded Therapeutics, GW Pharmaceuticals, ICON, IONIS Pharmaceuticals, Lundbeck, Stoke Therapeutics, and Supernus Pharmaceuticals. She received fees for non-CME/CE services directly from a commercial interest or their agents (e.g., speakers bureaus) from Advicenne, Biocodex, GW Pharmaceuticals, Nutricia, Shire, UCB, and Zogenix. She has been a contracted researcher for GW Pharmaceuticals and Zogenix. She has European FP7 grants, European Joint Programme on Rare Diseases. 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.

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