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Future opportunities for research in rescue treatments

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Abstract

Clinical studies of rescue medications for seizure clusters are limited and are designed to satisfy regulatory requirements, which may not fully consider the needs of the diverse patient population that experiences seizure clusters or utilize rescue medication. The purpose of this narrative review is to examine the factors that contribute to, or may influence the quality of, seizure cluster research with a goal of improving clinical practice. We address five areas of unmet needs and provide advice for how they could enhance future trials of seizure cluster treatments. The topics addressed in this article are: (1) unaddressed end points to pursue in future studies, (2) roles for devices to enhance rescue medication clinical development programs, (3) tools to study seizure cluster prediction and prevention, (4) the value of other designs for seizure cluster studies, and (5) unique challenges of future trial paradigms for seizure clusters. By focusing on novel end points and technologies with value to patients, caregivers, and clinicians, data obtained from future studies can benefit the diverse patient population that experiences seizure clusters, providing more effective, appropriate care as well as alleviating demands on health care resources.

KEYWORDS

benzodiazepines, clinical trials, rescue medication, seizure clusters, seizures

1 | INTRODUCTION

A seizure cluster (acute repetitive seizure) describes a series of distinct seizures separated by short interictal periods that occur over a span of 24 h.[1] At present, however, no specific definition has been adopted.[2] (See Haut and Nabbout, _Recognizing Seizure Clusters in the Community: The Path to Uniformity and Individualization in Nomenclature and Definition_ for more details on components defining seizure clusters.[3]) All rescue medications for seizure clusters utilize benzodiazepines, with rectal and intranasal formulations approved by the US Food and Drug Administration

(FDA), whereas oral formulations have been used off-label. (See Gidal and Detyniecki, _Rescue Therapies for Seizure Clusters: Pharmacology and Target of Treatments_ for more details regarding clinical trial information for approved rescue medications of seizure clusters.[4]) Clinical studies of rescue medications for seizure clusters are often focused on specific populations, which may affect the generalizability of the results, and they are designed to satisfy regulatory requirements. There is an unmet need to evaluate rescue medications and to determine how these are integrated with other strategies that are utilized for seizure cluster management in clinical practice.

What follows is a narrative review of questions of relevance to clinicians, patients, and caregivers/care partners, and although terminology for specific seizure conditions (e.g., seizure clusters are not recognized by the European Medicines Agency as a discrete condition) and the approved medications for those conditions may differ across regions, these concepts offer future opportunities for research. Each question is addressed with the data available, along with expert insights and discussions. The intent is that future studies will answer these queries, resulting in improved quality of care for all patients with epilepsy who experience seizure clusters.

Key Points
- Seizure cluster studies are designed to address regulatory requirements, which may not be representative of clinical practice
- Future studies should involve broad inclusion criteria consistent with the patient population that would use rescue medication
- Seizure cluster control for a 24-h period is a critical end point for these types of studies
- Devices used for seizure detection, evaluation, treatment, prediction, and prevention of seizure clusters could improve study quality

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2 | WHICH PREVIOUSLY UNADDRESSED OR UNDERUTILIZED END POINTS SHOULD BE PURSUED IN FUTURE STUDIES?

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2.1 | Primary end point

Seizure clusters have been associated with emergency-related hospitalizations and risk of progression to status epilepticus with potential associated mortality risk.[5,6] Successful control would be expected to reduce this medical burden, leading to improvements in quality of life (QoL) for patients and caregivers.[7] Therefore, prompt and durable control of the seizure cluster for 24 h as well as safety are the essential end points. The 24-h duration of control is critical in providing reassurance that the seizure cluster has been terminated, thus affording the patient and caregiver the opportunity to resume daily activities with less concern about a recurrence. Primary end points that focus on the magnitude of improvement compared with no treatment may be appropriate in studies that include patients with diverse seizure cluster characteristics and treatment objectives. Safety end points that address the maximum number of rescue doses in a 24-h period or how soon a second dose can be administered following a recurrence would be of value to both clinicians and families.

2.2 | Secondary end points

2.2.1 | Outcomes related to seizure cluster control

Secondary outcomes associated with seizure cluster control could provide a more comprehensive picture of rescue medication effectiveness and acceptance. These outcomes include ease of use (rated by patient, caregiver, or others [e.g., school nurse]), acceptance by patient, return to baseline activity/level of functioning, number of clusters requiring use of a second dose or timing of repeated doses, number of seizures in a cluster after treatment, and/or other events (e.g., emergency medical services [EMS] code, emergency department [ED] visit) following treatment or the initial seizure (Table 1). It is important for time-based outcomes to determine a clinically meaningful duration of time between events. For example, a time to next seizure of 4 h might still result in continued anticipatory anxiety over the potential for recurrence. The determination of minimal, clinically important thresholds (e.g., 12 h, 24 h) requires further investigation. Another set of outcomes is the absence of secondary events (particularly EMS call or ED visit), which could be compared with patients who

TABLE 1 Outcomes related to seizure cluster control

Outcomes
1. Number of doses (e.g., proportion of clusters for which a second dose is used)
2. Changes in dose frequency or requirements over time
3. Time to next dose (if given in same 24-h period)
4. Time to next seizure or delay in time to next seizure
5. Time from start of first seizure in cluster or cluster recognition to administration of medicine—influence on seizure cluster control over 24 h (e.g., number of seizures occurring in a cluster prior to treatment)
6. Time to resumption of normal activity
7. Seizure cluster interval (e.g., seizure cluster frequency change from weekly to monthly)
8. Duration of seizures within a cluster
9. Reduction in antiseizure medication use
10. Use of emergency medical services or the emergency department
11. Ease of use (patient, caregiver)
12. Acceptance by patient

do not receive rescue medication or in the same patient from a baseline period prior to treatment (e.g., 6 months, 1 year). Correlating the type of seizure(s) in the cluster with treatment outcomes would also be of interest. The development and validation of a scale to assess seizure cluster severity with and without treatment, which could include several characteristics of the cluster (e.g., seizure number and length, interval between seizures in a cluster, interval between clusters [Seizure cluster interval]) and show changes in an individual or group, might capture useful data of importance to patients and families.

2.2.2 | Clinical, quality of life, pharmacoeconomic outcomes

The effectiveness of seizure cluster control—the primary end point—is intertwined with a number of important outcomes that affect patients and caregivers. For example, outcomes of injury or mortality could be representative of the quality of seizure cluster control. Although seizure clusters have been reported to negatively impact patient mood, independence, and the ability to participate in daily activities,[8] there is no validated QoL instrument designed to measure the specific burden of seizure clusters (e.g., anxiety, mood, fear), which would be anticipated to align with the effectiveness of seizure cluster control. Finally, because seizure clusters are associated with emergency-related hospitalizations,[5] the rates of hospitalizations over time could be suggestive of seizure cluster control.

2.2.3 | Long-term safety and effectiveness

Chronic benzodiazepine use can lead to a reduction in its physiological effects (i.e., tolerance),[9] and a proportion of patients that utilize rescue medication also receive daily benzodiazepine treatment (e.g., clobazam in Lennox-Gastaut syndrome).[10] Identifying potential effects with differing concomitant medications is important in establishing the long-term safety and effectiveness of rescue medication. The effects of long-term use of intermittent benzodiazepine treatment of seizure clusters have not been fully explored. The effectiveness of some rescue medications over extended durations (24 h)[11] is suggestive of additional mechanisms apart from bioavailability alone. Evaluation of seizure cluster interval over time could provide an expanded perspective of seizure cluster control (Table 1).

Transient, modest change in cognitive function has been reported with benzodiazepine use, with more rapid onset (minutes) and restoration of function noted with intravenous diazepam administration as compared to rectal.[12] Therefore, a suitable time course for the expected

or potential changes in cognitive function must be determined relative to the route of administration in order to design a cognitive assessment strategy. The timing of cognitive assessments should be considered relative to the postictal state as well. Moreover, the suitability of cognitive assessments for functional domains, such as those associated with memory, concentration, and motor function, would have to be evaluated relative to baseline function in the study population. Patient-centered outcomes might include the ability and time needed to return to some daily activities or no longer requiring caregiver supervision (e.g., caregiver can return to prior activities). The development of a scale to report patient and/or caregiver satisfaction with time to recovery could provide additional information regarding patient- or caregiver-perceived functional status.

2.2.4 | Specific patient subgroups

Analyses of patient subgroups are crucial in obtaining a clear evaluation of an agent's effectiveness and safety. For example, treatments that require active participation (i.e., a conscious patient) may be more suitable for patients that experience prolonged aura or focal aware seizure onset. Prolonged seizures, including those that are difficult to distinguish from seizure clusters, as well as rapid repetitive seizures, may benefit from intranasal, intramuscular, or rectal formulations of midazolam or diazepam, or from inhaled alprazolam. Nonrapid repetitive seizures (e.g., clusters with recovery between seizures) would be suited for oral disintegrating clonazepam, sublingual lorazepam solution, buccal midazolam, oral diazepam, or lorazepam tablet or liquid. (See Gidal and Detyniecki, *Rescue Therapies for Seizure Clusters: Pharmacology and Target of Treatments* for information on rescue medications.[4]) Other analyses of possible treatment subgroups include those by underlying condition (e.g., encephalopathies, catamenial seizure clusters, complex febrile seizures) and frequency (e.g., more/fewer than two events per month). Differences in outcomes according to self-administration versus caregiver administration would be important to characterize, especially in patients who experience prolonged auras or focal aware seizures. Assessing the ability of rescue medication to shorten individual seizure duration in those patients with prolonged seizures would also be of value to clinicians and patients.

2.2.5 | Composite end points

The use of composite end points that could consist of the outcomes discussed above (e.g., seizure occurrence by time of day, pharmacoeconomics, QoL), especially those

that include patient, family, and caregiver experiences and beliefs regarding rescue medication, could provide more meaningful information than traditional end points. Composite end points that incorporate these different groups could include patient- and family-centered questions: Is treatment better than no treatment or emergency department visit? Do they want to continue with this treatment? Which treatment option would the family prefer? Other questions could be focused on outcomes important to professional caregivers (e.g., school nurse, long-term care facility staff), including preferred formulations or routes of administration and time to resumption of normal activities.

2.3 | Other considerations and limitations of prior studies

2.3.1 | Seizure cluster definition

Seizure cluster definitions are varied; therefore, the seizure cluster definition must be considered carefully during the design phase of the study. Specifically, how many seizures per episode constitute a seizure cluster and what is the total duration of the cluster (i.e., will it span 6, 12, or 24 h; 2 or 3 days)? A 12- to 24-h time period for children and adults, respectively, has been proposed as a critical window of time for when the majority of seizures are most likely to take place.[13] Statistical methods, such as the web-based ClusterCalc algorithm, that can account for a patient's baseline seizure frequency to detect true seizure clusters not attributed to random fluctuation (differentiate from natural seizure variation) may provide a more individualized definition.[14]

2.3.2 | Patient selection

To preserve the quality of the study, even at the expense of increased variability within the sample, it would be prudent not to exclude subjects based on prior status epilepticus, specific seizure type (e.g., focal, tonic, atypical absence, and myoclonic seizure clusters), high seizure frequency, age group (e.g., infants or young children), concomitant treatments, or epileptic encephalopathies (Lennox-Gastaut syndrome, Dravet syndrome). Maintaining the heterogeneity of the population allows for broader applicability of findings.

2.3.3 | Time frame considerations relative to seizure treatment

It is important to recognize that most seizures associated with a cluster are self-limiting and of short duration (a few minutes).[15] Therefore, an end point of

seizure termination would present a challenge due to the number of patients needed to treat. Although there is an urgency to terminate the seizure for patients and caregivers, the value of these data should be weighed against the challenges of obtaining the data during the development of the study design. As a practical matter, studies of seizure clusters typically measure termination of the cluster rather than the duration of a single seizure. Providing additional data, such as how many seizures occurred after the rescue was given, would help inform treatment options for families (i.e., not just the need for a second dose). This contrasts with studies of prolonged seizures, which can last for several minutes and would be more amenable to the outcomes of individual seizure termination.

2.3.4 | How to measure adherence with rescue medication

Determining adherence with treatments for unpredictable conditions possesses certain challenges. For example, some caregivers may not see a need to interrupt seizure clusters, which could affect the use of rescue medication. Conventional approaches include counting pills or devices and pharmacy records to assess adherence; however, these approaches are not well suited for rescue medications. Adherence to rescue medication for treating asthma has been studied using electronic medication monitors (EMMs), which can reveal when a medicine has been used.[16,17] The ability to integrate EMMs into smart device applications,[18] such as a seizure diary, could allow for improved, albeit indirect, adherence monitoring of rescue medication. Another approach would be to compare the number of refills with seizure cluster history recorded in the seizure diary over a specified time period. If partial adherence is documented, the rationale for treating only certain seizure clusters, rather than all, may inform future trials or allow strategies to improve patient care.

2.3.5 | Other questions for clinical trials

Another consideration for clinical trial design is how to address the natural variability in seizure cluster occurrence as well as triggers, such as illness, alcohol use, and changes in medication and sleeping patterns, which could contribute to noise in a study.[1] In addition, it would be helpful to know if the rescue efficacy is the same regardless of whether the cluster was spontaneous or provoked. Studies to date have not incorporated the consideration of changes in QoL. Improvements in QoL are key outcomes with respect to treatment efficacy and have been assessed by various scales[19–22]; however, there is no validated,

seizure cluster–specific instrument for assessing QoL for either patient or caregiver. A survey to assess the ease of use and patient/caregiver satisfaction could be an important evaluation. Optimal time to administration, medication errors, safety events related to the agent or route of administration, and the specific reasons for patient withdrawal are all crucial to an appropriate interpretation of efficacy and safety profiles.

3 | HOW CAN DEVICES POTENTIALLY ENHANCE CLINICAL TRIALS OF PHARMACOLOGIC TREATMENT FOR SEIZURE CLUSTERS AND PROVIDE CLINICALLY USEFUL RESULTS TO CLINICIANS, PATIENTS, AND CAREGIVERS/ CARE PARTNERS?

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The objective assessment of seizure cluster onset and duration can be difficult to ascertain, with caregivers often reporting individual patterns imprecisely. A technology to accurately assess these parameters may be possible with the development of seizure detection devices, which could improve the characterization of seizure clusters in clinical trials and guide the implementation of therapy.[23]

3.1 | Seizure detectors

Instruments for seizure detection utilize both invasive and noninvasive technologies. Currently, responsive neurostimulation (RNS) is the only neurostimulation device that directly assesses abnormal electrographic activity.[24] However, RNS has limited spatial sampling, and patient-specific detection settings programmed on the device may not capture all seizures.[25] Few patients with seizure clusters are suited for RNS[26]; thus, benefits with this device would be limited to a relatively small patient population. Sub-scalp electroencephalography (EEG) is a less invasive instrument and can be configured to work with smart applications and cloud networks.[27,28] Machine-learning algorithms can be paired with this technology to enhance seizure detection. Artifact from large muscle movements of the head (e.g., chewing) can impact data quality,[27] but artifacts can be removed by filtering and regression or by decomposing the EEG data into other domains.[29] The combination of EEG with video provides a more comprehensive analysis.[30] Moreover, video-based devices that can be utilized at home exhibit good performance during nighttime detection.[31]

Noninvasive seizure detection devices couple smart applications (including machine-learning algorithms) with multiple noninvasive modalities, such as accelerometry, heart rate, electromyography, electrodermography, and bed movement (reviewed by Shum and Friedman, 2021).[32–35] These are designed primarily to detect tonic-clonic seizures, and although performance is not well characterized, the field of noninvasive seizure detection is rapidly evolving.[35]

3.2 | Smart devices and apps

Seizure detectors could have roles in clinical development of pharmacological treatments for seizure clusters. These devices could increase the likelihood of prompt administration of medication in tonic-clonic seizures. In addition, cognitive function tests, heart rate, movement, and seizure timing can be measured by some of these devices and can provide additional data that could be used to determine treatment response and return to baseline. App systems that utilize seizure detectors can help identify seizure types and triggers using postictal surveys conducted on smart devices after cognitive recovery from seizures.[36]

Cognitive tests[37] customized to the patient's developmental or cognitive profile could be used to evaluate cognitive recovery following seizures (e.g., test for alertness, progressing to matching patterns in short-term memory puzzles). Thus the time course for a return to normal function could be determined as well as whether normal cognition was attained interictally. Return to normal responsiveness during seizure clusters could be determined and serve as a guide for selecting rescue medications, e.g. for spaced out versus rapid repetitive seizures. A short cognitive scale could be developed that the caregiver could utilize at specified times and standardized in a protocol to evaluate clusters. However, this may be difficult for caregivers to deliver while assisting in treating cluster seizures and testing responsiveness and recovery with smart devices may be more reliable.

Seizure detection devices could complement seizure action plans and acute seizure action plans. (See Patel and Becker, *Introduction to Use of an Acute Seizure Action Plan for Seizure Clusters and Guidance for Implementation* for more details regarding acute seizure action plans.[38]) Seizure detection devices can notify caregivers of a seizure,[37] potentially improving response times, likelihood of seizure termination, and better characterization of the seizure/seizure cluster (e.g., start time, duration). Seizure detectors could prompt medication administration or electrical stimulation at defined intervals and could be customized according to the patient's individual patterns.

Goals for seizure detection devices are low false detection (alarm) rates and the ability to differentiate between epileptic and nonepileptic seizures. A major challenge for

non-EEG seizure detectors is the detection of focal unaware seizures. Devices that combine modalities with individualized detection algorithms may have sensitivity to non-motor seizures (e.g., electrodermal activity, EEG, behavior).[39,40]

4 | WHAT TYPES OF TOOLS OR METHODS WOULD BE NEEDED TO SUPPORT FUTURE STUDIES OF SEIZURE CLUSTER PREDICTION AND PREVENTION?

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4.1 | Variables to assess

4.1.1 | Cyclical nature of epilepsy

Recent evidence suggests that seizure timing in epilepsy exhibits cyclical characteristics (e.g., daily, multi-day, yearly) and does not occur by chance alone.[41] Interictal epileptiform activity can fluctuate cyclically over multiple time scales,[42] helping to define periods of high and low seizure risk.[43] Increasing interictal epileptiform activity over days is associated with seizures or seizure clusters.[41] Prediction of a seizure cluster could provide an opportunity to prepare for, and potentially even begin, rescue treatment. There are several factors that could be involved in cycles of interictal epileptiform activity, such as circulating metabolites or hormones, endogenous/external cues, and patient-specific biological clock mechanisms. These types of assessments may be suitable to better characterize and predict seizure clusters.

4.1.2 | Triggers and biomarkers

Biological rhythms have been characterized in sleep patterns and endocrine physiology, which could be exploited to predict when seizure clusters may happen. Interictal epileptiform discharges (IEDs) can occur during sleep, with greater IEDs noted in non–rapid eye movement versus rapid eye movement sleep.[44] Sleep deprivation can lead to increased IEDs and the occurrence of seizures.[44,45] In contrast, greater durations of sleep have been associated with a lower probability of seizure in some people with epilepsy.[46] Although sleep–wake cycles operate in a circadian pattern, sleep duration and insomnia have both been reported to exhibit multi-day variation, and variation can be unique to the individual.[47,48]

Multi-day variation has been described for some hormones, such as sex steroids (estradiol, testosterone),

aldosterone, and cortisol[49–51]; as such, hormones are potentially useful biomarkers for seizure. Cortisol response to stress has been reported to be higher in people with epilepsy who are prone to stress,[52,53] and seizures and IEDs have been associated with cortisol levels in these patients.[52,53] In contrast, long-term (multi-day) seizure patterns have been observed in both male and female patients,[43] which could suggest that sex steroid fluctuations do not fully explain seizure patterns. Neurosteroids, such as allopregnanolone and tetrahydrodeoxycorticosterone, can alter γ-aminobutyric acid subtype A (GABA$_A$) receptor function, which can influence excessive neuroexcitation,[54] and low levels of allopregnanolone have been associated with seizure.[55] An approach to further elucidating relationships between hormones and seizures would be to sample hormone status in patients with RNS or subscalp EEG and to examine hormone levels during brain states of high and low seizure risk. These studies would increase our understanding of the phenomena but may have limited bedside utility.

4.1.3 | External and endogenous cues

External cues (e.g., light–dark cycles) are involved in regulation of the circadian rhythm via direct retinal innervation to the suprachiasmatic nucleus.[56] There are no obvious cues that regulate (or operate on) multi-day cycles (e.g., 7-day, 21-day); however, an endogenous cue is likely.[57,58] Other external cues, such as abrupt weather changes (atmospheric pressure, air humidity), may also contribute to seizure occurrence.[59]

4.2 | Methods for evaluation

Seizure diary data can be used independently or in combination with data obtained from devices to evaluate seizure risk. Seizure diaries have been used to track patient self-assessment of seizure risk in addition to seizure events (e.g., counts, duration), which have been used to predict seizures up to 24h in advance as well as for characterizing seizure cycles.[60–62] Qualitative assessment of mood fluctuations and cognitive function could potentially be investigated for use as markers of brain activity and possible transitions to high seizure risk. In addition, chronic EEG (RNS and subscalp and video-EEG) can be used for seizure evaluation.[24] Subscalp EEG could be of value for future studies because it may be more practical to scale and have greater brain coverage than RNS.[24] Comparing intracranial RNS data with concurrent subscalp EEG could help characterize the sensitivity of subscalp EEG for epileptiform activity.

4.3 | Methods for prediction

Seizure prediction is challenging owing to the heterogeneity of epilepsy, and the best device options currently are invasive and cannot be widely utilized. Nevertheless, longitudinal study designs would be appropriate to adequately characterize seizure risk patterns over time. A model (statistical or machine learning) could be developed based on RNS or subscalp EEG data and the associated outcomes in a patient cohort. Then the model could be used for seizure prediction for that same cohort over a follow-up period and validated on a separate cohort. Several longitudinal studies have used implanted EEG devices for seizure forecasting,[63,64] yielding effective forecasting models, with better-than-chance forecasts obtained up to 3 days prior to seizures in some individuals.[63] The addition of seizure diary information, biomarkers, and machine-learning methods could optimize the model. Limitations include poor generalizability owing to a narrow patient population with these devices. However, advances in seizure forecasting with wearable devices may circumvent these limitations in the future.[37,65]

An important question is what value seizure forecasting holds for the patient. Would there be an identifiable threshold for seizure risk (e.g., 25%, 50%, 75%) that would warrant a change in the patient's daily routine or initiation of abortive therapy? Moreover, the ability to estimate seizure risk may have unprecedented ethical and medico-legal implications.[66]

4.4 | Methods for prevention

Reductions in seizure frequency with long-term neurostimulation suggest that the actions of neurostimulation (vagus nerve stimulation [VNS], RNS, and deep brain stimulation [DBS]) can result in less excitable brain states. Although the exact mechanisms are unclear, interictal neurostimulation induces network reorganization (neuroplasticity) over time.[67,68] Indeed, reductions in median seizure frequency reached 66% at year 6[69] and 75% over a 9-year period in an RNS cohort.[70] Similar rates of reduction in seizure frequency were noted in patients following 7 years of thalamic DBS,[71] whereas median seizure frequency was reduced by 66% in patients with VNS following 3 years of exposure.[72] Although evidence is limited (e.g., case reports), VNS has also been associated with reductions in frequency, intensity, or termination of seizure clusters.[73,74] Neurostimulation (RNS, DBS, VNS) has also shown effectiveness in reducing the frequency of, or terminating, status epilepticus,[75–77] with a systematic review of VNS reporting termination of status epilepticus in 74% of patients following acute implantation of the device.[77]

Neurostimulator settings (charge density, frequency) can stabilize or stimulate transitions to brain states of low seizure risk[78]; however, these are preset by the clinician. A device that could modulate stimulator settings in real time according to specific brain states and conditions (e.g., seizure cluster) would advance the field, resulting in an instrument that could be used for both prevention and termination of an event.

5 | COMPARED WITH CURRENT STUDY DESIGNS FOR TREATMENT OF SEIZURE CLUSTERS, WHAT IS THE POTENTIAL VALUE OF OTHER DESIGNS TO PROVIDE DATA IMPORTANT TO CLINICIANS, PATIENTS, AND CAREGIVERS/CARE PARTNERS?

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Randomized, double-blind, placebo-controlled trials are considered the gold standard of evidence; however, considerations specifically relevant to studies pertaining to prolonged seizures and seizure clusters should inform study design.

5.1 | Placebo control

A placebo control arm is appropriate for studies examining new end points or new types of seizure emergencies for which there is no precedent or approved therapy. Placebo would be unethical if an established treatment is available, especially if withholding appropriate treatment could result in harm to the patient. However, some types of seizure clusters have low risk of harm (e.g., those that consist of only a few short seizures spaced across the course of a day that are not expected to progress to status epilepticus), and a placebo would provide the greatest chance to detect separation between experimental treatments. In contrast, placebo would be ethically problematic for patients with epileptic encephalopathies (Lennox-Gastaut syndrome, Dravet syndrome) or complex febrile seizures when there is an accepted need for and standard of treatment. In these patients, an active-control arm would be appropriate for patient safety and care, although these trials have inherent limitations.[79]

5.2 | Active control

Compared with placebo control, active control ensures that all patients receive therapy. However, the end point must

be selected carefully as it could be difficult to detect separation between the treatment and active control. Primary end points should be those that are most likely to reveal separation between treatments, such as seizure recurrence, need for second dose, recovery from dose, QoL, and caregiver preference. Other comparisons of which the magnitude of separation is uncertain would be defined as secondary end points. The active control should be accepted by clinicians, which can be a limitation, as a consensus on appropriate active control, including dosage, may be elusive.[79]

5.3 | Design considerations

Rescue medication should be prescribed to all patients with a history of seizure clusters.[2] Therefore, initial inclusion and exclusion criteria should be broad (e.g., patients who have prolonged seizure clusters or predictable cluster patterns; see Section 2.3.2 for further discussion on inclusion/exclusion criteria). Some of the selection criteria could be driven by the pharmacology of the rescue drug. However, studies of rescue medications must enroll patients who meet a threshold of treatable events so that study objectives can be adequately assessed. Where feasible, the addition of a screening or baseline period (e.g., 8 weeks) to the traditional study design would allow all patients to provide historical or baseline data to meet a threshold for treatable events. Event types used for screening would be specific to the treatment under consideration; however, some examples related to seizure cluster could be:

- Patients who have two seizures in a predefined period (e.g., 6 or 12 h) will experience a third seizure.
- If a seizure lasts 3 min, it will go on for 10 min.
- An aura or prodrome with particular characteristics will precede a seizure cluster.

- Seizure duration or number of seizures after index seizure (or treatment).
- Cluster onset from sleep (vs. daytime or wake onset).

The effect of sleep duration on seizure clusters is of interest, and multisensory wearable devices (e.g., smart watches) possess the functionality to track sleep and are widely available. However, these devices are relatively new, and few have been validated for sleep detection.[80] The threshold for treatable events can be more stringent for initial trials. In a phase 2 trial, for example, the screening period could identify patients who experience a high proportion of treatable events (e.g., 80% of total events are treatable events), whereas less stringent thresholds could be used for larger phase 3 studies (e.g., 50% are treatable events). Patients not meeting inclusion criteria could remain in the safety analysis, providing information on community use.

The use of a placebo can control for the confounding effects of seizures that terminate spontaneously. Patients could be randomized to treatment or control arms using the established standard of care as a second dose for seizure clusters that persist following an initial dose of the experimental treatment or placebo control (Figure 1). Common routes of administration for treatment and control would allow for blinding of both investigators and patients. The use of electronic diaries and electronic patient-reported outcomes may help in conducting a single-blind study when using interventions with different routes of administration.

5.3.1 | Other design types

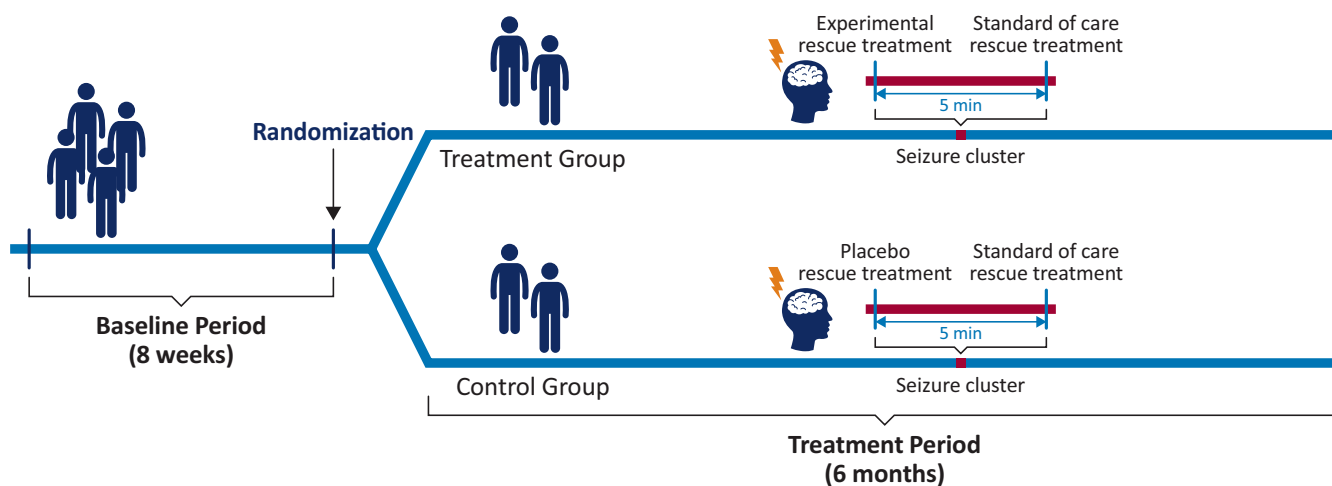Other study designs may have limitations with respect to seizure clusters. Placebo run-in involves administration

FIGURE 1 Potential study design for rescue medication.

of placebo to all subjects during a screening period to determine adherence to treatment[81]; however, its usefulness may be questionable for intermittent conditions, and there could be an increased risk of harm for some patients owing to the potential for progression to status epilepticus.[5] In addition, studies with placebo comparison may have intentional or unintentional unblinding that may introduce bias.[82] Delayed start designs examine the effect of treatment as compared to control/placebo but also characterize the disease-modifying effect over time after those who receive control/placebo are transitioned to the experimental treatment.[83] The stochastic nature of seizure clusters, though, may not be well suited for this design. Multi-arm crossover[84] could be a reasonable choice for studies of seizure clusters but would require patients with relatively frequent seizure clusters, potentially affecting generalizability, and trial duration would have to be sufficient to detect separation between treatments. There are few appropriate data sets available for historical control studies for seizure clusters. In addition, studies conducted over different time periods are likely to have dissimilar patient populations, including different concomitant medications. Moreover, historical controls may not be available for novel types of seizure exacerbations or end points.

5.4 | Electronic medical records

Electronic medical records (EMRs; electronic health records) are convenient to use and contain a wide variety and large quantity of patient data; however, patient records can be imperfect (missing data, incorrect codes). Changes in health care providers and insurance can lead to gaps in the patient record. When selecting patients for studies of seizure clusters using EMRs, it is important to consider strategies (e.g., excluding patients with no activity in the medical record for 6 months) to minimize the impact of missing and invalid data, as these can substantially alter study results. An International Classification of Diseases (ICD) code was recently created for seizure clusters (acute repetitive seizures; 8A67),[85] which along with physician/chart notes and prescription information, may lead to greater utilization of medical records for seizure cluster research in the future. Integration of data from patient diary apps and detection devices into the EMR would provide an improved means of tracking response to therapy or lack thereof.

5.4.1 | Patient selection

Inclusion criteria using EMR data could include emergency room visits for seizures, status epilepticus, or seizure clusters along with prescription information. Prescription for rescue may differ from usage, however, due to the variability of occurrence of seizure clusters and because some patients may have prescriptions for peace of mind rather than anticipated use.

5.4.2 | Outcomes

Data from EMRs can be used to determine health care utilization and hospitalizations. An outcome of rescue medication failure would most likely require physician/chart notes, and it is unclear how consistently rescue medication failure is recorded in this format. Nevertheless, the newly added ICD code for seizure clusters may create new opportunities to examine the effectiveness of rescue medication through EMRs.

6 | LOOKING INTO FUTURE TRIALS, WHAT NEW PARADIGMS DO YOU SEE EMERGING FOR TREATMENT OF SEIZURE CLUSTERS? WHAT ARE THE UNIQUE CHALLENGES?

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6.1 | Seizure cluster prediction and detection of increased vulnerability

The goal of a prediction device or algorithm is to anticipate the majority of seizure clusters (see Section 4 for an expanded discussion on methods for prediction). In addition to predicting the initial seizure of a seizure cluster, a device could also be used to assess the likelihood that more seizures will occur. This could advance clinical care as patients and their families are left weighing the need for rescue medication versus the odds that further seizures are likely to occur. Challenges include balancing false-positive and false-negative rates and the effect of patient age, seizure type, and other factors on accuracy. For example, a method using machine learning has demonstrated some success forecasting focal- and generalized-onset seizures using noninvasive devices (e.g., wrist), with alerts provided approximately half an hour in advance in those patients.[86] In addition, absence seizures have been detected using a noninvasive EEG-wearable device that utilizes machine learning,[87] as well as with a glasses-monitoring eye tracker method.[88] Modalities such as photoplethysmography, electrocardiography, respiration, motion, electrodermal

activity, electromyography, and EEG (especially sub-scalp EEG),[27,65,89–94] along with additional data sets for algorithm training, will improve prediction and detection performance of wearable devices.

6.2 | Predicting response to treatment

The potential for a particular treatment to successfully abort a seizure cluster is unpredictable for the individual. Some patients are nonresponsive to benzodiazepines but instead respond to sodium channel blockers, or there could be responses specific to certain benzodiazepines but not others. Functional magnetic resonance imaging, EEG (e.g., high-frequency oscillations), heart rate variability, or other biomarkers could provide insights as to the potential of success for some therapies.[65,95,96]

6.3 | Disease modification

Neurostimulation is associated with increasing reduction in seizure frequency with longer exposure, and it would be useful to determine if neurostimulation influences the frequency of seizure clusters, number of seizures per cluster, interval between seizures in a cluster and interval between clusters, and other end points. It is also unclear if or how long the effects of long-term neurostimulation may persist in the absence of neurostimulation. Evidence supports an indirect mechanism, perhaps manifested by alterations in functional connectivity, independent of direct stimulation events.[67,68] The impact of rescue medication use over time to modify future seizure clusters, including the duration of seizure cluster interval, is poorly understood and worthy of future investigation. Other experimental treatments that hold the therapeutic potential to modify seizure clusters may include cell transplants, which involve the transplantation of inhibitory interneurons; gene therapy, including optogenetics; and new drugs and delivery systems, such as infusion pumps that deliver drugs directly to the bloodstream, brain ventricle, and/or cerebrospinal fluid.[97–100]

7 | CONCLUSION

New clinical studies utilizing new study end points or technology have the potential to improve care for patients with seizure clusters. Patients with epileptic encephalopathies (e.g., Dravet syndrome) are typically not included in clinical studies of rescue medication. However, they constitute a clinically relevant proportion of patients with seizure clusters who could benefit from more inclusive designs. Federally supported extramural grants should be utilized to support research of special groups and new technologies. The intent of rescue medication is to empower patients, family members, and caregivers to manage care for seizure clusters outside of an emergency department setting, similar to at-home management of acute exacerbations of asthma with inhalation agents. By focusing on novel end points and technologies with value to patients, caregivers, and clinicians, data obtained from future studies can benefit the diverse patient population that experiences seizure clusters, providing more effective, appropriate care as well as alleviating demands on health care resources.

Study Consortium received payments for research services performed by Dr Friedman from Axcella, Biogen, Cerevel, Crossject, Engage Pharmaceuticals, Eisai, Lundbeck, Pfizer, SK Life Science, Xenon, and Zynerba. In addition, he has served as a paid consultant for Eisai and Neurelis, Inc. He has received travel support from Medtronics, Eisai, and the Epilepsy Foundation. He has received research support from the Centers for Disease Control and Prevention (CDC), National Institute for Neurological Disorders and Stroke (NINDS), Epilepsy Foundation, Empatica, Epitel, UCB Inc., and Neuropace. He serves on the scientific advisory board for Receptor Life Sciences. He holds equity interests in Neuroview Technology and Receptor Life Sciences. He received royalty income from Oxford University Press. Dr Krauss has served as a consultant/advisor for Adamas, Eisai, Otsuka, and Shire. He has received research support from Biogen, SK Life Science, UCB Pharma, and Upsher-Smith Laboratories, Inc. Dr Rao has served as a consultant for NeuroPace, Inc., manufacturer of the RNS System. Dr Sperling has received compensation for speaking at continuing medical education programs from Medscape, Projects for Knowledge, International Medical Press, and UCB Pharma. He is an advisor for scientific publications for Neurelis, Inc. He consults for Medtronic with payments to Thomas Jefferson University. He has received research support from Eisai Inc.; Medtronic; Neurelis, Inc.; SK Life Science; Takeda; Xenon; Cerevel; UCB Pharma; Janssen; Equilibre; and Engage Pharmaceuticals. He has received royalties from Oxford University Press and Cambridge University Press. Dr Carrazana is an employee of and has received stock and stock options from Neurelis, Inc. Dr Rabinowicz is an employee and has received stock options from Neurelis, Inc. 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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REFERENCES
1. Jafarpour S, Hirsch LJ, Gainza-Lein M, Kellinghaus C, Detyniecki K. Seizure cluster: definition, prevalence, consequences, and management. Seizure. 2019;68:9–15.
2. Buchhalter J, Shafer PO, Buelow JM, French JA, Gilchrist B, Hirsch LJ, et al. Preferred practices for rescue treatment of seizure clusters: a consensus-driven, multi-stakeholder approach. Epilepsy Behav. 2021;117:107836.
3. Haut SR, Nabbout R. Recognizing seizure clusters in the community: the path to uniformity and individualization in nomenclature and definition. Epilepsia. 2022.
4. Gidal B, Detyniecki K. Rescue therapies for seizure clusters: pharmacology and target of treatments. Epilepsia. 2022;63(Suppl. 1):S34–S44.
5. Haut SR, Shinnar S, Moshe SL. Seizure clustering: risks and outcomes. Epilepsia. 2005;46(1):146–9.
6. Neligan A, Noyce AJ, Gosavi TD, Shorvon SD, Kohler S, Walker MC. Change in mortality of generalized convulsive status epilepticus in high-income countries over time: a systematic review and meta-analysis. JAMA Neurol. 2019;76(8):897–905.
7. Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. Epilepsia. 2011;52(12):2168–80.
8. Penovich PE, Buelow J, Steinberg K, Sirven J, Wheless J. Burden of seizure clusters on patients with epilepsy and caregivers: survey of patient, caregiver, and clinician perspectives. Neurologist. 2017;22(6):207–14.
9. Higgitt A, Fonagy P, Lader M. The natural history of tolerance to the benzodiazepines. Psychol Med Monogr Suppl. 1988;13:1–55.
10. Yang LP, Scott LJ. Clobazam: in patients with Lennox-Gastaut syndrome. CNS Drugs. 2012;26(11):983–91.
11. Sperling MR, Wheless JW, Hogan RE, Dlugos D, Cascino GD, Liow K, et al. Use of second doses of Valtoco(R) (diazepam nasal spray) across 24 hours after the initial dose for out-of-hospital seizure clusters: results from a phase 3, open-label, repeat-dose safety study. Epilepsia. 2022;63(4):836–43.
12. Cloyd JC, Lalonde RL, Beniak TE, Novack GD. A single-blind, crossover comparison of the pharmacokinetics and cognitive effects of a new diazepam rectal gel with intravenous diazepam. Epilepsia. 1998;39(5):520–6.
13. Dreifuss FE, Rosman NP, Cloyd JC, Pellock JM, Kuznicky RI, Lo WD, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. N Engl J Med. 1998;338(26):1869–75.
14. Chiang S, Haut SR, Ferastraoaru V, Rao VR, Baud MO, Theodore WH, et al. Individualizing the definition of seizure clusters based on temporal clustering analysis. Epilepsy Res. 2020;163:106330.
15. Ferastraoaru V, Schulze-Bonhage A, Lipton RB, Dumpelmann M, Legatt AD, Blumberg J, et al. Termination of seizure clusters is related to the duration of focal seizures. Epilepsia. 2016;57(6):889–95.
16. De Keyser HEH, Kaye L, Anderson WC, Gondalia R, Theye B, Szefler SJ, et al. Electronic medication monitors help determine adherence subgroups in asthma. Respir Med. 2020;164:105914.
17. Hoch H, Kempe A, Brinton J, Szefler S. Feasibility of medication monitoring sensors in high risk asthmatic children. J Asthma. 2019;56(3):270–2.

18. Faisal S, Ivo J, Patel T. A review of features and characteristics of smart medication adherence products. Can Pharm J. 2021;154(5):312–23.

19. Berto P. Quality of life in patients with epilepsy and impact of treatments. Pharmacoeconomics. 2002;20(15):1039–59.

20. Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia. 1998;39(1):81–8.

21. Baker GA, Smith DF, Jacoby A, Hayes JA, Chadwick DW. Liverpool seizure severity scale revisited. Seizure. 1998;7(3):201–5.

22. Duncan JS, Sander JW. The Chalfont seizure severity scale. J Neurol Neurosurg Psychiatry. 1991;54(10):873–6.

23. Steriade C, Sperling MR, DiVentura B, Lozano M, Shellhaas RA, Kessler SK, et al. Proposal for an updated seizure classification framework in clinical trials. Epilepsia. 2022;63:565–72.

24. Rao VR. Chronic electroencephalography in epilepsy with a responsive neurostimulation device: current status and future prospects. Expert Rev Med Devices. 2021;18:1093–105.

25. Thomas GP, Jobst BC. Critical review of the responsive neurostimulator system for epilepsy. Med Devices. 2015;8:405–11.

26. NeuroPace, Inc. NeuroPace RNS system patient manual. Mountain View, CA: NeuroPace, Inc. 2013. [cited 28 Oct 2021]. Available from https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100026C.pdf

27. Stirling RE, Maturana MI, Karoly PJ, Nurse ES, McCutcheon K, Grayden DB, et al. Seizure forecasting using a novel sub-scalp ultra-long term EEG monitoring system. Front Neurol. 2021;12:713794.

28. Duun-Henriksen J, Baud M, Richardson MP, Cook M, Kouvas G, Heasman JM, et al. A new era in electroencephalographic monitoring? Subscalp devices for ultra-long-term recordings. Epilepsia. 2020;61(9):1805–17.

29. Islam MK, Rastegarnia A, Yang Z. Methods for artifact detection and removal from scalp EEG: a review. Neurophysiol Clin. 2016;46(4–5):287–305.

30. Goodwin E, Kandler RH, Alix JJ. The value of home video with ambulatory EEG: a prospective service review. Seizure. 2014;23(6):480–2.

31. Kandler R, Ponnusamy A, Wragg C. Video ambulatory EEG: a good alternative to inpatient video telemetry? Seizure. 2017;47:66–70.

32. Poh MZ, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Sabtala MC, et al. Convulsive seizure detection using a wrist-worn electrodermal activity and accelerometry biosensor. Epilepsia. 2012;53(5):e93–7.

33. Kim T, Nguyen P, Pham N, Bui N, Truong H, Ha S, et al. Epileptic seizure detection and experimental treatment: a review. Front Neurol. 2020;11:701.

34. Beniczky S, Conradsen I, Wolf P. Detection of convulsive seizures using surface electromyography. Epilepsia. 2018;59(Suppl 1):23–9.

35. Shum J, Friedman D. Commercially available seizure detection devices: a systematic review. J Neurol Sci. 2021;428:117611.

36. Ge A, Gutierrez EG, Wook Lee S, Shah S, Carmenate Y, Collard M, et al. Seizure triggers identified postictally using a smart watch reporting system. Epilepsy Behav. 2022;126:108472.

37. Brinkmann BH, Karoly PJ, Nurse ES, Dumanis SB, Nasseri M, Viana PF, et al. Seizure diaries and forecasting with wearables: epilepsy monitoring outside the clinic. Front Neurol. 2021;12:690404.

38. Patel AD, Becker DA. Introduction to use of an acute seizure action plan for seizure clusters and guidance for implementation. Epilepsia. 2022;63(Suppl. 1):S25–S33.

39. Poh MZ, Loddenkemper T, Swenson NC, Goyal S, Madsen JR, Picard RW. Continuous monitoring of electrodermal activity during epileptic seizures using a wearable sensor. Annu Int Conf IEEE Eng Med Biol Soc. 2010;2010:4415–8.

40. Zijlmans M, Flanagan D, Gotman J. Heart rate changes and ECG abnormalities during epileptic seizures: prevalence and definition of an objective clinical sign. Epilepsia. 2002;43(8):847–54.

41. Karoly PJ, Rao VR, Gregg NM, Worrell GA, Bernard C, Cook MJ, et al. Cycles in epilepsy. Nat Rev Neurol. 2021;17(5):267–84.

42. Karoly PJ, Freestone DR, Boston R, Grayden DB, Himes D, Leyde K, et al. Interictal spikes and epileptic seizures: their relationship and underlying rhythmicity. Brain. 2016;139(Pt 4):1066–78.

43. Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, et al. Multi-day rhythms modulate seizure risk in epilepsy. Nat Commun. 2018;9(1):88.

44. Halasz P, Bodizs R, Ujma PP, Fabo D, Szucs A. Strong relationship between NREM sleep, epilepsy and plastic functions—a conceptual review on the neurophysiology background. Epilepsy Res. 2019;150:95–105.

45. Lanigar S, Bandyopadhyay S. Sleep and epilepsy: a complex interplay. Mo Med. 2017;114(6):453–7.

46. Dell KL, Payne DE, Kremen V, Maturana MI, Gerla V, Nejedly P, et al. Seizure likelihood varies with day-to-day variations in sleep duration in patients with refractory focal epilepsy: a longitudinal electroencephalography investigation. EClinicalMedicine. 2021;37:100934.

47. Wong SN, Halaki M, Chow CM. The periodicity of sleep duration—an infradian rhythm in spontaneous living. Nat Sci Sleep. 2013;5:1–6.

48. Vignatelli L, Masetti S, Amore M, Laterza C, Mattarozzi K, Pierangeli G, et al. Insomnia cycling with a 42-day infradian period: evidence for two uncoupled circadian oscillators? Sleep Med. 2010;11(4):343–50.

49. Celec P, Ostatnikova D, Putz Z, Kudela M. The circalunar cycle of salivary testosterone and the visual-spatial performance. Bratisl Lek Listy. 2002;103(2):59–69.

50. Celec P, Ostatníková D, Hodosy J, Skokňová M, Putz Z, Kúdela M. Infradian rhythmic variations of salivary estradioland progesterone in healthy men. Biol Rhythm Res. 2006;37(1):37–44.

51. Rakova N, Juttner K, Dahlmann A, Schroder A, Linz P, Kopp C, et al. Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. Cell Metab. 2013;17(1):125–31.

52. Allendorfer JB, Heyse H, Mendoza L, Nelson EB, Eliassen JC, Storrs JM, et al. Physiologic and cortical response to acute psychosocial stress in left temporal lobe epilepsy—a pilot cross-sectional fMRI study. Epilepsy Behav. 2014;36:115–23.

53. van Campen JS, Hompe EL, Jansen FE, Velis DN, Otte WM, van de Berg F, et al. Cortisol fluctuations relate to interictal epileptiform discharges in stress sensitive epilepsy. Brain. 2016;139(Pt 6):1673–9.

54. Miziak B, Chroscinska-Krawczyk M, Czuczwar SJ. Neurosteroids and seizure activity. Front Endocrinol (Lausanne). 2020;11:541802.

55. Meletti S, Lucchi C, Monti G, Giovannini G, Bedin R, Trenti T, et al. Decreased allopregnanolone levels in cerebrospinal fluid obtained during status epilepticus. Epilepsia. 2017;58(2):e16–20.

56. Hastings MH, Maywood ES, Brancaccio M. Generation of circadian rhythms in the suprachiasmatic nucleus. Nat Rev Neurosci. 2018;19(8):453–69.

57. Saggio ML, Crisp D, Scott JM, Karoly P, Kuhlmann L, Nakatani M, et al. A taxonomy of seizure dynamotypes. eLife. 2020;9:e55632.

58. Rao VR, Leguia MG, Tcheng TK, Baud MO. Cues for seizure timing. Epilepsia. 2021;62(Suppl 1):S15–31.

59. Rakers F, Walther M, Schiffner R, Rupprecht S, Rasche M, Kockler M, et al. Weather as a risk factor for epileptic seizures: a case-crossover study. Epilepsia. 2017;58(7):1287–95.

60. Privitera M, Haut SR, Lipton RB, McGinley JS, Cornes S. Seizure self-prediction in a randomized controlled trial of stress management. Neurology. 2019;93(22):e2021–31.

61. Karoly PJ, Eden D, Nurse ES, Cook MJ, Taylor J, Dumanis S, et al. Cycles of self-reported seizure likelihood correspond to yield of diagnostic epilepsy monitoring. Epilepsia. 2021;62(2):416–25.

62. Goldenholz DM, Goldenholz SR, Romero J, Moss R, Sun H, Westover B. Development and validation of forecasting next reported seizure using e-diaries. Ann Neurol. 2020;88(3):588–95.

63. Proix T, Truccolo W, Leguia MG, Tcheng TK, King-Stephens D, Rao VR, et al. Forecasting seizure risk in adults with focal epilepsy: a development and validation study. Lancet Neurol. 2021;20(2):127–35.

64. Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. Lancet Neurol. 2013;12(6):563–71.

65. Karoly PJ, Stirling RE, Freestone DR, Nurse ES, Maturana MI, Halliday AJ, et al. Multiday cycles of heart rate are associated with seizure likelihood: an observational cohort study. EBioMedicine. 2021;72:103619.

66. Hegde M, Chiong W, Rao VR. New ethical and clinical challenges in "closed-loop" neuromodulation. Neurology. 2021;96(17):799–804.

67. Khambhati AN, Shafi A, Rao VR, Chang EF. Long-term brain network reorganization predicts responsive NEURO-STIMULATION outcomes for focal epilepsy. Sci Transl Med. 2021;13(608):eabf6588.

68. Kokkinos V, Sisterson ND, Wozny TA, Richardson RM. Association of closed-loop brain stimulation neurophysiological features with seizure control among patients with focal epilepsy. JAMA Neurol. 2019;76(7):800–8.

69. Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015;84(8):810–7.

70. Nair DR, Laxer KD, Weber PB, Murro AM, Park YD, Barkley GL, et al., on behalf of the RNS System LTT Study. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology 2020;95(9):e1244–56.

71. Salanova V, Sperling MR, Gross RE, Irwin CP, Vollhaber JA, Giftakis JE, et al. The SANTE study at 10 years of follow-up: effectiveness, safety, and sudden unexpected death in epilepsy. Epilepsia. 2021;62(6):1306–17.

72. Kawai K, Tanaka T, Baba H, Bunker M, Ikeda A, Inoue Y, et al. Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry. Epileptic Disord. 2017;19(3):327–38.

73. Morita M, Fujimoto A, Okanishi T, Nishimura M, Sato K, Kanai S, et al. Vagus nerve stimulation therapy improved refractory epilepsy secondary to acute encephalitis with refractory, repetitive partial seizures (AERRPS). Interdiscip Neurosurg. 2017;9:76–9.

74. Muchamad GR, Hanaya R, Maruyama S, Yonee C, Hosoyama H, Baba Y, et al. Effects of vagus nerve stimulation on sustained seizure clusters: a case report. NMC Case Rep J. 2021;8(1):123–8.

75. Ernst LD, Krause KL, Kellogg MA, Raslan AM, Spencer DC. Novel use of responsive neurostimulation (RNS system) in the treatment of super refractory status epilepticus. J Clin Neurophysiol. 2019;36(3):242–5.

76. Sobstyl M, Stapinska-Syniec A, Rylski M. Deep brain stimulation for the treatment of refractory and super-refractory status epilepticus. Seizure. 2020;81:58–62.

77. Dibue-Adjei M, Brigo F, Yamamoto T, Vonck K, Trinka E. Vagus nerve stimulation in refractory and super-refractory status epilepticus—a systematic review. Brain Stimul. 2019;12(5):1101–10.

78. Chiang S, Khambhati AN, Wang ET, Vannucci M, Chang EF, Rao VR. Evidence of state-dependence in the effectiveness of responsive neurostimulation for seizure modulation. Brain Stimul. 2021;14(2):366–75.

79. Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: practical issues and specific cases. Ann Intern Med. 2000;133(6):464–70.

80. Lujan MR, Perez-Pozuelo I, Grandner MA. Past, present, and future of multisensory wearable technology to monitor sleep and circadian rhythms. Front Digit Health. 2021;3:721919.

81. Davis CE, Applegate WB, Gordon DJ, Curtis RC, McCormick M. An empirical evaluation of the placebo run-in. Control Clin Trials. 1995;16(1):41–50.

82. Ortiz V, Ellenberg SS, Weinberg EM. Blinding in clinical trials for chronic liver diseases. Semin Liver Dis. 2021;41(2):163–71.

83. D'Agostino RB Sr. The delayed-start study design. N Engl J Med. 2009;361(13):1304–6.

84. Sibbald B, Roberts C. Understanding controlled trials. Crossover trials. BMJ. 1998;316(7146):1719–20.

85. International Classification of Diseases, 11th Edition. World Health Organization. [cited 2022 Feb 3]. Available from: https://www.who.int/standards/classifications/classification-of-diseases

86. Meisel C, El Atrache R, Jackson M, Schubach S, Ufongene C, Loddenkemper T. Machine learning from wristband sensor data for wearable, noninvasive seizure forecasting. Epilepsia. 2020;61(12):2653–66.

87. Swinnen L, Chatzichristos C, Jansen K, Lagae L, Depondt C, Seynaeve L, et al. Accurate detection of typical absence seizures in adults and children using a two-channel electroencephalographic wearable behind the ears. Epilepsia. 2021;62(11):2741–52.

88. Mitsuhashi T, Sonoda M, Iwaki H, Sakakura K, Asano E. Detection of absence seizures using a glasses-type eye tracker. Clin Neurophysiol. 2021;132(3):720–2.

89. van Andel J, Ungureanu C, Aarts R, Leijten F, Arends J. Using photoplethysmography in heart rate monitoring of patients with epilepsy. Epilepsy Behav. 2015;45:142–5.

90. Vandecasteele K, De Cooman T, Gu Y, Cleeren E, Claes K, Paesschen WV, et al. Automated epileptic seizure detection

based on wearable ECG and PPG in a hospital environment. Sensors (Basel). 2017;17(10):2338.

91. Ahmed A, Ahmad W, Khan MJ, Siddiqui SA, Cheema HM. A wearable sensor based multi-criteria-decision-system for real-time seizure detection. Annu Int Conf IEEE Eng Med Biol Soc. 2017;2017:2377–80.

92. Meritam P, Ryvlin P, Beniczky S. User-based evaluation of applicability and usability of a wearable accelerometer device for detecting bilateral tonic-clonic seizures: a field study. Epilepsia. 2018;59(Suppl 1):48–52.

93. Onorati F, Regalia G, Caborni C, Migliorini M, Bender D, Poh MZ, et al. Multicenter clinical assessment of improved wearable multimodal convulsive seizure detectors. Epilepsia. 2017;58(11):1870–9.

94. Beniczky S, Conradsen I, Henning O, Fabricius M, Wolf P. Automated real-time detection of tonic-clonic seizures using a wearable EMG device. Neurology. 2018;90(5):e428–34.

95. Xiao F, Koepp MJ, Zhou D. Pharmaco-fMRI: a tool to predict the response to antiepileptic drugs in epilepsy. Front Neurol. 2019;10:1203.

96. Engel J Jr, Bragin A, Staba R. Nonictal EEG biomarkers for diagnosis and treatment. Epilepsia Open. 2018;3(Suppl 2):120–6.

97. Harward SC, Southwell DG. Interneuron transplantation: a prospective surgical therapy for medically refractory epilepsy. Neurosurg Focus. 2020;48(4):E18.

98. Cela E, Sjostrom PJ. Novel optogenetic approaches in epilepsy research. Front Neurosci. 2019;13:947.

99. Cook M, Murphy M, Bulluss K, D'Souza W, Plummer C, Priest E, et al. Anti-seizure therapy with a long-term, implanted intra-cerebroventricular delivery system for drug-resistant epilepsy: a first-in-man study. EClinicalMedicine. 2020;22:100326.

100. Tan T, Watts SW, Davis RP. Drug delivery: enabling technology for drug discovery and development. iPRECIO® micro infusion pump: programmable, refillable, and implantable. Front Pharmacol. 2011;2:44.