

## SPECIAL ISSUE ARTICLE

## Consequences: Bench to home

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**Abstract**

Seizure clusters (also referred to as acute repetitive seizures) consist of several seizures interspersed with brief interictal periods. Seizure clusters can break down  $\gamma$ -aminobutyric acidergic (GABAergic) inhibition of dentate granule cells, leading to hyperactivation. Functional changes to GABA<sub>A</sub> receptors, which play a vital neuroinhibitory role, can include altered GABA<sub>A</sub> receptor subunit trafficking and cellular localization, intracellular chloride accumulation, and dysregulation of proteins critical to chloride homeostasis. A reduction in neuroinhibition and potentiation of excitatory neurotransmission in CA1 pyramidal neurons represent pathological mechanisms that underlie seizure clusters. Benzodiazepines are well-established treatments for seizure clusters; however, there remain barriers to appropriate care. At the clinical level, there is variability in seizure cluster definitions, such as the number and/or type of seizures associated with a cluster as well as the interictal duration between seizures. This can lead to delays in diagnosis and timely treatment. There are gaps in understanding between clinicians, their patients, and caregivers regarding acute treatment for seizure clusters, such as the use of rescue medications and emergency services. This lack of consensus to define seizure clusters in addition to a lack of education for appropriate treatment can affect quality of life for patients and place a greater burden on patient families and caregivers. For patients with seizure clusters, the sense of unpredictability can lead to continuous traumatic stress, during which patients and families live with a heightened level of anxiety. Clinicians can affect patient quality of life and clinical outcomes through improved seizure cluster education and treatment, such as the development and implementation of a personalized seizure action plan as well as prescriptions for suitable rescue medications indicated for seizure clusters and instructions for their proper use. In all, the combination of targeted therapy along with patient education and support can improve quality of life.

**KEYWORDS**

quality of life, seizure action plan, seizure clusters, seizures, status epilepticus

## 1 | SEIZURE CLUSTERS FROM BENCH TO HOME

Seizure clusters (acute repetitive seizures) may be characterized by two or more seizures that have a pattern distinguishable from a patient's normal seizure pattern and that are separated by brief interictal states.<sup>1</sup> Seizure clusters are associated with greater odds for status epilepticus and greater rates of morbidity, mortality, and sudden unexplained death in epilepsy (SUDEP) as compared to nonclustering seizures.<sup>2-6</sup> Therefore, prompt treatment designed to attenuate seizure activity is critical to prevent severe outcomes.

Seizure cluster management is a continuum from development of therapies, notably benzodiazepines,<sup>7</sup> to the creation and implementation of customized treatment protocols, such as a seizure action plan,<sup>8</sup> to ensure appropriate, individualized, timely care. This review is designed to provide the underlying molecular mechanisms of seizures and seizure clusters upon which therapies are targeted as well as the clinical implications for health care providers, family members, and caregivers. The dynamic nature of seizure cluster pathophysiology and patient care spans from bench science to clinical care and to patients and caregivers at home.

## 2 | PRECLINICAL/CLINICAL PATHOPHYSIOLOGY

Clinical literature suggests that seizure clusters occupy a space between a single seizure and status epilepticus. Treiman has considered seizure clusters as the first stage of status epilepticus.<sup>9</sup> In experimental animals, discrete seizures occur repeatedly before merging into a single, prolonged seizure or status epilepticus. It is important to recognize that this transition state is a critical opportunity to terminate or prevent status epilepticus. In experimental animals, benzodiazepines are highly effective at terminating seizure clusters.<sup>10</sup> However, once seizure clusters merge into prolonged seizures, they become less responsive to benzodiazepines.<sup>11</sup>

Here, we consider circuit and molecular mechanisms that convert seizure clusters into prolonged continuous seizures. Of note, data on the pathophysiology of status epilepticus are derived primarily from experimental models that have focused on the hippocampus because until recently, only a few neocortical-onset status epilepticus models, including one from our group,<sup>12</sup> were available. However, ongoing neocortical studies show that benzodiazepine resistance develops rapidly and excitatory transmission is enhanced in this model, and these features are

### Key Points

- Seizure cluster management requires the identification of molecular and clinical mechanisms that contribute to patient outcomes
- A breakdown in GABA<sub>A</sub> receptor-mediated neurotransmission underlies the pathophysiology of seizures and seizure clusters
- Varied definitions of seizure clusters, level of patient education, and provider knowledge are barriers to identifying at-risk patients
- Seizure action plans are designed to lead to consistent, appropriate responses to seizure clusters, supporting timely and effective care

similar to those observed in hippocampal-onset status epilepticus.

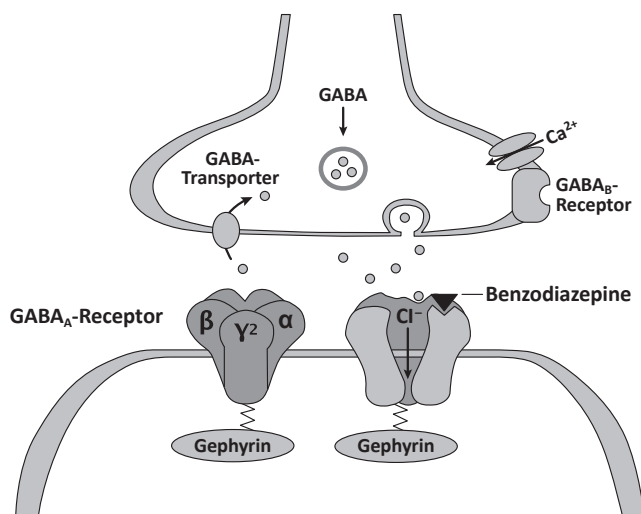
### 2.1 | Dentate gate

Most seizures are self-limiting because there are brain circuit, cellular, and molecular mechanisms designed to limit the flow of excessive neuronal activity. Hippocampal circuitry is informative because it is a common site of seizure origin, although its normal function is to encode memory, especially spatial memory.<sup>13</sup> Pathophysiological modification of memory storage can lead to seizures.<sup>14</sup> The primary input into the hippocampus is from the entorhinal cortex, which projects to the dentate gyrus via the perforant path. The dentate gyrus projects to CA3 pyramidal cells via mossy fibers, and CA3 neurons send Schaffer collaterals to CA1 pyramidal neurons. CA1 pyramidal neurons encode memory and generate seizures.<sup>15,16</sup> Rich interconnections of the entorhinal cortex with multiple cortical areas facilitate memory formation. However, we do not memorize most events within our stream of consciousness and sensation; thus, the dentate gyrus must filter out most sensory and affective information flowing into the entorhinal cortex before it reaches the CA1 hippocampus.<sup>16</sup>

The dentate gyrus is a pattern separator or gate, preventing the flow of excessive neuronal activity into the hippocampus proper.<sup>17-19</sup> Several cellular and circuit properties help perform this filtering function. Granule cells, which are weakly excitable,<sup>20</sup> receive a barrage of inhibitory inputs from a variety of  $\gamma$ -aminobutyric acidergic (GABAergic) interneurons.<sup>21</sup> GABAergic terminals are distributed around granule cell soma and dendrites in the molecular layer, with the most dense innervation in the

outer molecular layer.<sup>22</sup> Three chemically identified types of interneurons constitute the bulk of interneurons, those expressing parvalbumin, cholecystokinin, and somatostatin.<sup>21</sup> These interneurons are highly active, releasing the inhibitory neurotransmitter GABA, which activates extrasynaptic GABA<sub>A</sub> receptors, which further inhibit granule cells.<sup>23</sup>

GABA<sub>A</sub> receptors are pentameric, ligand-gated anion channels.<sup>24</sup> The subunits are derived from  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\pi$ ,  $\theta$ , and  $\rho$  gene families, some of which have multiple members, such as  $\alpha$ 1–6,  $\beta$ 1–3, and  $\gamma$ 1–3. The majority of receptors are composed of two  $\alpha$  subunits, two  $\beta$  subunits, and one  $\gamma$  or  $\delta$  subunit (Figure 1).<sup>24–27</sup> Receptor sensitivity to neurosteroids and benzodiazepines, such as diazepam, lorazepam, and midazolam, depends on receptor subunit composition.<sup>28</sup> Diazepam sensitivity requires a  $\gamma$ 2 subunit, and the relative affinity also depends on the  $\alpha$  subtype incorporated into the receptor.<sup>24</sup> The  $\delta$  subunit confers high neurosteroid sensitivity to the receptors. The  $\gamma$ 2 subunit is necessary for synaptic localization of the receptors, whereas GABA<sub>A</sub> receptors composed of the  $\delta$  subunit remain exclusively in the perisynaptic and extrasynaptic membranes.<sup>29</sup> Synaptic GABA receptors mediate fast inhibition in response to the high concentration of GABA released in the synaptic cleft, whereas extrasynaptic receptors respond to GABA spilled over from the synapses and contribute to persistent background inhibition, called tonic inhibition.<sup>23,24,30</sup>



**FIGURE 1**  $\gamma$ -Aminobutyric acid (GABA) neurotransmission. GABA<sub>A</sub> receptors are heteropentameric chloride channels. Benzodiazepine-induced modulation of GABA<sub>A</sub> receptor function requires expression of the  $\gamma$ 2 subunit in the channel complex. Republished with permission of the American Society for Pharmacology and Experimental Therapeutics, from Möhler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. *J Pharmacol Exp Ther*. 2002;300(1):2–8; permission conveyed through Copyright Clearance Center.

## 2.2 | Seizures open dentate gate by breaking down GABAergic inhibition

Seizures open the dentate gate.<sup>31,32</sup> Functional mapping studies demonstrate hyperactivation of dentate granule cells during the recurrent seizure stage.<sup>33</sup> When seizures arise in the CA1 region, they travel to the entorhinal cortex and stop because the dentate gyrus prevents their reentry into the hippocampus.<sup>31</sup> This phenomenon occurs in vivo and in vitro (slice experiments).<sup>34</sup> Detailed cellular mapping of dentate gyrus activation during recurrent seizures reinforces the notion of the dentate gate, with massive activation of granule cells when seizures become self-sustaining.<sup>33</sup>

Repeated seizures can break down GABAergic inhibition of dentate granule cells.<sup>35</sup> Multiple mechanisms lead to the disruption of inhibition, including altered receptor trafficking, accumulation of intracellular chloride ions, and dysfunction of interneurons. Seizures reduce and modify GABA<sub>A</sub> receptors on hippocampal neurons.<sup>36,37</sup> Neurotransmitter receptors, such as GABA<sub>A</sub> receptors, constantly move from the intracellular compartment to the neuronal surface membrane to synapses. Then they are endocytosed into the endosomes, and these processes allow dynamic modulation of inhibitory transmission.<sup>38</sup> A large number of studies show that seizures accelerate the endocytosis of GABA<sub>A</sub> receptors.<sup>35,39,40</sup> Seizures specifically enhance the endocytosis of synaptic GABA<sub>A</sub> receptors, reducing synaptic inhibition.<sup>35,41</sup> Benzodiazepines selectively enhance GABA-mediated synaptic inhibition but not extrasynaptic tonic inhibition. Therefore, benzodiazepines are ideal for reinforcing synaptic inhibition under assault from seizures.

GABA receptors allow the bidirectional passage of chloride ions across the neuronal membrane, depending on the membrane potential and the chloride reversal potential. Intracellular chloride accumulation makes chloride reversal potential more depolarized, and, if this reaches beyond the action potential threshold, GABA can be excitatory.<sup>42</sup> Seizure-induced accumulation of chloride aids the collapse of GABAergic inhibition in hippocampal neurons.<sup>37,43</sup> A low intracellular chloride ion concentration helps the inhibitory action of the neurotransmitter GABA.<sup>44</sup> In addition to intracellular immobile anions exercising Donnan forces, chloride transporters play an important role in maintaining the chloride equilibrium potential. The K<sup>+</sup>/Cl<sup>-</sup> cotransporter (KCC2) plays an important role in seizure-induced disruption of chloride homeostasis.<sup>45</sup> Recurrent seizures reduce KCC2 activity by dephosphorylating the protein.<sup>46</sup> Reduced KCC2 activity reduces the efficacy of GABAergic inhibition and may even convert it into an excitatory transmitter.<sup>43</sup>

### 2.3 | Seizure potentiates excitatory synaptic transmission in CA1 pyramidal neurons

As noted above, CA1 pyramidal neurons play an important role in encoding memory. This encoding is achieved in part through long-term potentiation (LTP) of excitatory glutamatergic synapses.<sup>47</sup> Seizures can potentiate excitatory synapses using mechanisms similar to LTP.<sup>48,49</sup> Fast excitatory transmission is mediated primarily by aminomethylphosphonic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors. A single seizure potentiates AMPA receptor-mediated excitatory transmission on specific CA1 pyramidal neurons.<sup>50</sup> In summary, repetitive seizures enhance excitatory transmission.

### 2.4 | Pathophysiology to patient care

Most seizures end by themselves because multiple brain mechanisms at the circuit, cellular, and molecular levels, such as AMPA- and NMDA-mediated transmission and altered purinergic transmission, act in concert to terminate them.<sup>51–55</sup> However, recurrent seizure episodes are dangerous because they break down natural GABAergic seizure-terminating mechanisms and initiate synaptic potentiation, which could trigger further seizures. Early treatment of recurrent seizures with benzodiazepines can break this vicious cycle. However, although benzodiazepines are effective at terminating seizure clusters, there remain challenges to timely treatment at clinical and patient levels. The following sections will describe clinician and patient perspectives as they relate to seizure cluster management, including those of clinical staff as well as family members and caregivers.

## 3 | IMPACT: CLINICAL PERSPECTIVE

Seizure clusters are dynamic events that vary from patient to patient. As such, clinical decisions related to rescue treatment must consider a multitude of factors, such as the patient's typical presentation (including response to treatment), as well as the patient's environment, care team, and other individuals who could be involved in patient care (coworkers, friends, etc.). Here, we will discuss issues related to management of seizure clusters from a clinician's point of view, highlighting key concepts along with potential barriers to appropriate care (Table 1).

### 3.1 | Identifying patients at risk

There is a clinical need to identify patients at risk of seizure clusters, which involves coordinated efforts from patients, patient family members and friends, emergency medical services, and health care providers. Seizure clusters are associated with morbidity and mortality,<sup>3–5</sup> including SUDEP for patients with an underlying tendency for SUDEP.<sup>56</sup> Patients who experience seizure clusters commonly have refractory epilepsy and higher rates of hospitalization,<sup>1,2</sup> leading to greater health care costs and demands on health care resources. See Haut and Nabbout, *Recognizing Seizure Clusters in the Community: The Path to Uniformity and Individualization in Nomenclature and Definition* for more details regarding the clinical implications of seizure clusters.<sup>57</sup>

A number of practical barriers to identifying patients at risk for seizure clusters exist. There is no clear consensus on the definition of a seizure cluster, which complicates identification in the limited time that clinicians have for patient consultations. The number of seizures, type, and time interval between seizures (4–24 h or more) differ across seizure cluster definitions.<sup>2,58–62</sup> Recall of information in and around the time of seizure can be limited for patients with seizure clusters. Seizures that occur during sleep may not be fully characterized or recognized.<sup>63,64</sup> Moreover, some patients and their families may not understand the seriousness of the occurrence of seizure clusters,<sup>60</sup> managing care on an as-needed basis without an organized plan. Current health care practices may also represent a barrier. For example, decisions to refer patients from primary care to specialized epilepsy/neurology care can influence timeliness of appropriate treatment.<sup>65</sup>

Strategies to address these barriers include improved communication between health care providers to help increase colleagues' awareness of seizure clusters to better identify at-risk patients. Similarly, a comprehensive record of seizure history is critical for identification of seizure clusters. Health care providers should identify efficient, easy-to-implement methods to gather patient information on seizure patterns, frequencies, and characteristics of seizure clusters. Moreover, patient and caregiver education on seizure clusters can improve seizure cluster identification.

### 3.2 | Management and self-management of seizure clusters

Seizure action plans (SAPs) and specific acute SAPs (ASAPs) are designed to improve patient outcomes, decrease patient anxiety, reduce overuse of emergency medical services, and

**TABLE 1** Clinical perspective

Issues	Barriers	Solutions
Identification of at-risk patients	<ul style="list-style-type: none"> <li>• Variable definitions of seizure clusters</li> <li>• Details of seizure events can be limited (poor recall, events during sleep)</li> <li>• Delay in referral to specialized care (epileptologist/neurologist)</li> </ul>	<ul style="list-style-type: none"> <li>• Provide user-friendly methods to record and/or track seizure clusters</li> <li>• Improve communication between health care providers to increase awareness of seizure clusters</li> </ul>
Management of seizure clusters	<ul style="list-style-type: none"> <li>• Lack of recommendations (rescue medication) and support for health care providers</li> <li>• Patient reluctance to disclose condition</li> </ul>	<ul style="list-style-type: none"> <li>• Customize SAPs/ASAPs (for patient and seizure cluster)</li> <li>• Explain the purpose and function of SAPs/ASAPs, rescue medications</li> <li>• Simplify formats of SAPs/ASAPs, integrate with smart applications/devices (e.g., seizure diaries)</li> </ul>
Rescue medication	<ul style="list-style-type: none"> <li>• Patient uncertainty over role of rescue medication</li> <li>• Access to rescue medication (authorization, cost, pharmacy)</li> <li>• Concerns or preferences over route of administration (intranasal, rectal, buccal)</li> </ul>	<ul style="list-style-type: none"> <li>• Evaluate suitability of rescue medication on a case-by-case basis</li> <li>• Educate patients, caregivers, and family members on the purpose and proper use of the prescribed rescue medication (include in SAP/ASAP)</li> </ul>

Abbreviations: ASAP, acute SAP; SAP, seizure action plan.

facilitate sharing of treatment guidance.<sup>8,66,67</sup> SAPs provide instructions related to seizure care and management (rescue and daily medications) as well as detailed patient and contact information, whereas an ASAP is concisely focused on the rescue protocol and provides emergency procedures.<sup>8</sup> See Patel and Becker, *Introduction to Use of an Acute Seizure Action Plan for Seizure Clusters and Guidance for Implementation* in this supplement for more details regarding ASAPs.<sup>68</sup> In facilities that care for people with epilepsy who also have intellectual disabilities, direct, easy-to-understand instructions for seizure cluster care like those found in an ASAP could improve recognition of patient-specific manifestations (e.g., types of seizures that are likely to represent the initial seizure in a cluster), shorten response times for treatment, and reinforce optimal response and care provided by multiple staff members, including support staff with limited medical training. In the community setting, some adult patients may be familiar with seizure first aid, but their care partners may benefit from written specific and comprehensive guidance. Importantly, SAPs are underused in adult patients compared with pediatric patients,<sup>60</sup> who can be asked to have SAPs on file in school settings.<sup>69</sup>

There are several practical barriers to greater utilization of SAPs/ASAPs by adult patients who practice self-care. First, there is a lack of recommendations and support tools for health care providers, particularly guidance on incorporation of newly approved treatment options. Adults who are living and working in community settings may be reluctant to inform peers or employers about their SAP/ASAP owing to concerns over public perception of their condition.<sup>70,71</sup> Ideally, an SAP/ASAP should be designed for use in a particular setting, such as home, work, or in a care facility. For example, a general SAP may be

used less if deemed unsuitable for a specific work environment. Colleagues and employers may have reservations or concerns over their involvement in the SAP (easier to call emergency medical services), as well as misperceptions of safety concerning rescue medications. In addition, current recommendations for SAPs can be labor-intensive<sup>69</sup> and can be perceived as difficult to implement owing to time constraints.

There are steps that can be taken to address barriers to implementation of SAPs/ASAPs. Development of SAPs/ASAPs should be consistent, with seizure clusters included as part of the process. Action plans can be designed to balance the privacy rights of adults with the need to provide appropriate care during a seizure cluster. For example, patient preference to minimize use of an ambulance or taking social considerations into choice of rescue therapy can inform development of the action plan. A collaborative development process involving patient, (with adult patients' consent) caregiver or care partner, and clinician can help improve relevance of the plan, leading to patients and caregivers being more willing to use and share their plans with others (e.g., colleagues at work, babysitters, grandparents).<sup>8</sup> Colleagues, including emergency department staff and first-line health care providers (e.g., primary care providers), should also be educated on the role of SAPs/ASAPs. Integration of SAPs/ASAPs into electronic medical record systems facilitates appropriate access by health care providers, such as those in the emergency department, while complying with privacy legislation.<sup>72</sup> Processes should be streamlined for ease of use and effectiveness, such as simplified formats, accessibility, use of plain language, color coding, checkboxes for

common items, and illustrations.<sup>8</sup> SAPs/ASAPs should be reviewed regularly and updated as necessary, including when pediatric patients transition to adult care and when patients experience a change in their seizure pattern. Other improvements, such as electronic SAPs/ASAPs with integration of a seizure diary and personalization, can facilitate use of these plans. SAPs/ASAPs can also empower patients and caregivers and reduce their need to call health care providers.<sup>8</sup>

Rescue medications are key interventions included in SAPs/ASAPs for patients with seizure clusters.<sup>8,69</sup> Despite their benefits, rescue medications (e.g., benzodiazepines) appear to be underused,<sup>73</sup> which may contribute to overuse of emergency medical services.<sup>2</sup> Selection of a rescue medication should be customized to each patient, with consideration given to the safety and effectiveness with respect to seizure cluster duration. For patients in long-term care facilities who have physical limitations (e.g., wheelchair) or large patients who may be difficult to position correctly for treatment, considerations should be made with respect to route of administration. Rectal administration of rescue medication to someone in a wheelchair could represent a barrier to timely treatment. Moreover, the steps required for administration of some rescue treatments can be relatively extensive,<sup>74</sup> which can also represent barriers to use owing to the level of training needed by facility staff members to administer treatment. An inability to successfully administer rescue medication could lead to reduced effectiveness due to poor absorption of the drug,<sup>75</sup> potentially requiring extended care of the seizure cluster and limiting the availability of staff to care for other patients' needs. Alternative routes of administration have been approved (i.e., two intranasal formulations) or are in development (e.g., buccal or intrapulmonary formulations) and represent an important area of ongoing research.<sup>76,77</sup> (See Gidal and Detyniecki, *Rescue Therapies for Seizure Clusters: Pharmacology and Target of Treatments* in this supplement for more details regarding current and future therapies.<sup>78</sup>) Alternative routes could alleviate concerns from staff members over administration of treatment for patients who require long-term care. In all, rescue medications for seizure clusters may reduce health care utilization and improve management in the community setting and long-term care facilities by giving patients and caregivers a greater sense of control.<sup>8</sup>

Despite the importance of rescue medications, a key component of effective SAPs/ASAPs, there remain barriers to use of rescue medications. There are gaps in the understanding of seizure clusters and the role of rescue medications for treatment.<sup>60</sup> Other challenges for rescue medication exist, such as difficulties with insurance coverage, cost, need for prior authorization, and access through special pharmacies.<sup>79</sup> In the community setting, routes of

administration (e.g., rectal) can be important considerations, particularly for adult and adolescent patients.<sup>69,80,81</sup>

Health care providers can address these gaps and improve use of rescue medications through education and communication with colleagues across settings, including emergency department staff and first-line health care providers. Moreover, health care providers should carefully evaluate their patients for suitability of rescue medication treatment, considering their history, seizure patterns, use of rescue medications, and use of emergency medical services. Patient education on the role of rescue medication as a crucial component of the SAP or ASAP should be extended to include family members. Practical information on dosing and administration of rescue medications should be provided in the SAP or ASAP. If the patient has social concerns about their rescue medication, clinicians can discuss alternative medications and routes of administration with patients to determine whether a change in treatment may be warranted, which should be reflected in an updated SAP or ASAP.

### 3.3 | Clinician role

The clinician plays three vital roles in the overall supervision and administration of care for patients who experience seizure clusters. First, the clinician serves as a *communicator*, providing instructions and discussing patient goals. Second, the clinician serves as an *educator*, understanding and using treatments, including the role of the SAP or ASAP, with the intention of empowering patients. Third, the clinician serves a primary role as a *health care provider*, evaluating symptoms and seizure history to determine whether a diagnosis of seizure clusters is appropriate, prescribing medication, and guiding the development of the SAP or ASAP (including clear direction about when to use rescue medication). In all, the clinician seeks to reduce barriers to the identification of patients at risk of seizure clusters and to guide the appropriate use of SAPs/ASAPs with rescue medications to improve patient outcomes. However, to be successful, this process must reflect the perspectives of the patient and family or caregivers as well.

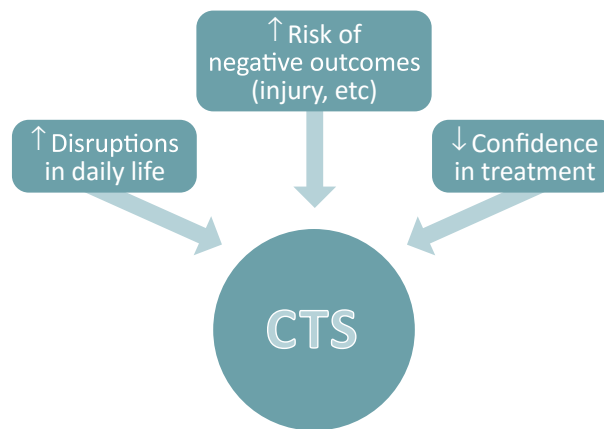
## 4 | IMPACT: FAMILY PERSPECTIVE

Seizure clusters can adversely affect various aspects of quality of life, such as the ability to plan and participate in activities, of both patients and caregivers. However, the degree to which seizure clusters affect quality of life can also vary according to disease severity. Here, we will

discuss implications of seizure clusters on quality of life in patients with frequent and infrequent seizure clusters.

In patients with frequent seizure clusters, the unpredictability of epilepsy results in a greater burden on patients and caregivers.<sup>60</sup> Increased seizure frequency leads to more disruptions throughout the day, and the ability to perform common daily activities becomes strained.<sup>60</sup> Moreover, frequent seizures are suggestive of greater disease severity, which has been associated with cognitive decline and risk of life-threatening events (e.g., injuries, aspiration pneumonia).<sup>82–84</sup> An inability to control seizure clusters can result in uncertainty about the efficacy of treatment decisions. For example, questions can arise about the efficacy of medications in patients with frequent seizures.<sup>85</sup> Patients and caregivers can encounter other questions when faced with an inability to control seizure clusters, such as the safety of additional doses of rescue medication, alternative medications with different routes of administration (e.g., rectal vs. nasal), doubts about medication delivery or absorption following an involuntary response (sneeze for nasal administration, defecation for rectal administration), and the use of emergency services.<sup>75,86–88</sup> Over time, this can lead to continuous traumatic stress (CTS).<sup>89</sup> In contrast to posttraumatic stress disorder, which is stress due to an event that happened in the past, CTS is a condition in which an individual lives at a heightened level of anxiety concerning future events. Seizure-associated CTS can damage a person's self-confidence to plan and engage in normal daily activities.<sup>60</sup> Specifically, patients can experience questions and insecurities over length of rest/recuperation, personal abilities and skills, future physical/mental/emotional challenges, public embarrassment (urination or defecation in public), and health care costs.<sup>60,90</sup> Trauma or judgment from witnesses of an event, especially one that involves emergency personnel, can contribute further to patient stress. In addition to experiencing stress over the challenges presented to patients, parents of children who have early life epilepsies along with other family members can experience chronic stress originating from a variety of other factors, such as medical care decisions specific to early life epilepsies, relationships (within and outside the family), and planning for the future.<sup>91</sup> In all, frequent seizure clusters can discourage patients and family from planning events and living their lives, resulting in a reactive day-to-day existence, whereby patients and family are surviving rather than thriving (Figure 2).

Seizure frequency has been associated with greater stigma and lower self-esteem, which contribute to reductions in health-related quality of life in people with epilepsy.<sup>92–94</sup> Patients with infrequent seizure clusters, along with their family members, can experience many of the same thoughts and feelings as those who deal with



**FIGURE 2** Outcomes associated with poor seizure cluster control for patients, care partners, and family members. CTS, continuous traumatic stress.

frequent seizure clusters, although the degree to which these feelings are experienced could vary. For example, some patients may experience less stress over rescue medications because these medications may play a smaller role in their daily management of the disease. However, some patients with infrequent seizure clusters may experience stress owing to the lack of familiarity with seizure cluster occurrence and management.

#### 4.1 | Challenges

As previously discussed, seizure cluster definitions are variable,<sup>2,59–62</sup> which can present barriers to appropriate treatment for patients and their families, just as it does to clinicians. Moreover, seizures are dynamic; patient signs and symptoms as well as the overall disease course can change over time, including the type and frequency of seizures within a seizure cluster. For example, a patient may start with a generalized tonic-clonic seizure, which could later taper into an atypical absence seizure. The variable nature of seizure clusters and the lack of a one-size-fits-all definition presents a substantial barrier to timely identification of seizure cluster patterns as well as treatments.

There remain other questions and concerns experienced by patients with seizure clusters and their families, such as the potential for brain damage, when to seek emergency care at a hospital, appropriate use of rescue medication outside the home, and use of an SAP or ASAP.<sup>60,88</sup> Moreover, gaps have been noted between clinicians' recommendations for action and patients' more passive seizure cluster management. For example, a survey of patients with seizure clusters, caregivers, and clinicians noted that approximately 79% of clinicians recommended rescue medication for a seizure

cluster, 67% recommended calling a doctor, and 61% recommended emergency services.<sup>60</sup> In contrast to clinicians, patients reported that they would do nothing (27%) during a seizure cluster, with only 24% replying that they would seek emergency care, 20% would call their doctor, and 20% would take rescue medication.<sup>60</sup> These findings underscore the challenges in patient and family adoption of clinically appropriate care for seizure clusters as recommended by physicians. The development and implementation of an SAP or ASAP could improve patient and family attitudes toward seizure cluster management.<sup>8</sup> However, patients and families may be unclear about what information to include in an SAP or ASAP, who should have access to it (e.g., employers), and how the SAP or ASAP should be executed. Nevertheless, although SAPs are underused by adult patients,<sup>60</sup> current evidence in pediatric patients suggests that SAPs could be beneficial in improving quality of life.<sup>67</sup> Taken together, improved patient–clinician communication, a standardized seizure cluster definition, and SAPs or ASAPs that incorporate seizure cluster-specific language could improve quality of life for patients with seizure clusters and their family members. Patient and family input are vital to the development of an effective, individualized SAP or ASAP.

## 5 | CONCLUSION: SEIZURE CLUSTERS FROM BENCH TO HOME

The mechanisms that lead to seizure clusters have implications for appropriate therapies and their implementation by health care providers as well as coordinating therapy with patients and caregivers. Because of the understanding of GABA<sub>A</sub> receptor expression and function, benzodiazepines are the mainstay of treatment for seizure clusters. However, clinicians, patients, and their families face barriers to seizure cluster identification and treatment. Clinical investigations are needed to identify factors that affect quality and timeliness of care received by patients and families as well as those that affect the delivery of care by nonspecialist health care providers. The development and use of a clearly defined, personalized SAP and ASAP can help ensure treatment to mitigate some of the important burdens that patients and their families face.

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### CONFLICT OF INTEREST

J.K. does not report any competing interests. L.L. is a consultant for Neurelis, SK Life Science, and Supernus Pharmaceuticals, and is a speaker for LivaNova. T.D.-S. is the Executive Director of the LGS Foundation and a consultant for the Chan Zuckerberg Initiative and Neurelis. 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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