

## SPECIAL ISSUE ARTICLE

# Seizure clusters: Practical aspects and clinical strategies to care for patients in the community

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Seizure clusters are a serious, yet often underdiagnosed and inadequately treated, occurrence in people with epilepsy. A challenge for both health care providers and patients is the lack of a cohesive integrated body of information examining the definitions, causes, consequences, and therapies for seizure clusters. This supplement aims to provide a practical resource about seizure clusters for both caregivers and people with epilepsy. To create a comprehensive informative view of this serious condition, this supplement integrates fundamental, translational, and clinical trial data with family insights, expert practical experience, and pharmacoeconomic approaches. Through this series of articles, the reader will be both more informed and more empowered to create, implement, and execute effective acute seizure action plans (ASAPs) that will likely reduce the serious medical and quality-of-life consequences associated with seizure clusters. This knowledge will enable the health care provider to communicate with and listen to patients and caregivers more effectively when discussing seizure control and safety.

The first article by Haut and Nabbout directly addresses the fundamental challenge that there is no universally agreed-upon definition for “seizure cluster,” either in clinical trials or in clinical practice. As such, reported prevalence of seizure clusters varies widely (13%–76%) among people with epilepsy, but these percentages indicate that this problem is clearly not a minor health issue. The various definitions used in clinical trials are reviewed, along with several clinical vignettes that illustrate the different

descriptions seen in seizure clusters. However, the authors point out that the lack of a classical standardized definition using seizure number and time periods allows the caregiver and patient to design a customized and individualized definition that can facilitate communication and care.

Next, Kapur, Long, and Dixon-Salazar examine the consequences of seizure clusters from multiple viewpoints: the molecular perspective of its pathophysiologic underlying mechanisms, the caregiver role in early identification and treatment, and finally the patient and family's view and approach to these alarming and anxiety-provoking events. Individual seizures are typically self-limited due to coordinated actions at multiple brain levels (circuit, cellular, and molecular). The recurrent seizures that define seizure clusters disrupt  $\gamma$ -aminobutyric acidergic (GABAergic) mechanisms while also initiating synaptic potentiation, enhancing the risk for further seizures. This article reviews basic science data supporting the importance of early treatment with benzodiazepines to disrupt the biological consequences of seizure clusters. The authors then address the role of the clinician in helping to reduce the clinical consequences of seizure clusters. By serving as a communicator, educator, and health care provider, the clinician can determine whether seizure clusters are occurring, develop an individualized ASAP, and prescribe the appropriate treatment modalities (e.g., benzodiazepines) for the patient. Finally, the authors point out that to fully minimize the consequences of seizure

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clusters, knowledge about the brain's mechanisms of initiation, propagation, and termination of seizures should be integrated with the health care providers' experience and skills along with the perspectives of the patient and family/caregivers. Enhanced patient–clinician communication and interaction (especially during the development of an individualized ASAP) are crucial for enhancing early recognition and effective treatment of a seizure cluster by patients and their families, which will in turn minimize the cluster's impact on quality of life and diminish the potential risk of any medical consequences.

A key document that integrates scientific knowledge of seizure clusters, health care provider clinical experience, and patient and family beliefs and understanding is the ASAP. The article by Patel and Becker first describes the use of a general seizure action plan as a key strategic tool in the chronic management of patients with epilepsy. In contrast, they point out that ASAPs are focused on how to deliver effective care during a seizure emergency. They describe the key aspects of developing a patient-specific ASAP (including patient-specific seizure details along with when and how to use rescue medications). They also identify important potential barriers that health care providers, patients, and their families face when developing ASAPs, along with approaches to address these challenges. Crucial features of successful ASAPs include that they are customized for the individual patient, are written in a clear and concise format, are practical and user friendly, and are developed to provide adequate education for both the patient and caregiver. To help with the time constraints providers face in developing and educating patients and families about the plan, it is proposed that customized ASAPs be created using a standardized template. Lastly, the authors recommend scientifically rigorous studies to fully determine the impact of SAPs and ASAPs on patient's and families' health and quality-of-life outcomes.

A key aspect of an ASAP is the choice of intervention or “rescue” medication. Benzodiazepines are the mainstay of initial rescue therapy for acute seizure clusters based on both their GABA<sub>A</sub> receptor activation mechanism and human clinical trial data. Gidal and Detyniecki review the data supporting the three benzodiazepine preparations currently approved by the US Food and Drug Administration—diazepam rectal gel (*Diastat*), intranasal midazolam (*Nayzilam*), and diazepam nasal spray (*Valtoco*)—for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy. Clinical trial data for benzodiazepine formulations used in other parts of the world for seizure clusters are also examined. Lastly, pharmacokinetic and pharmacodynamic characteristics of an ideal rescue medication are

discussed, coupled with a look at potential future rescue medications.

The development of a customized, patient- and family-friendly, practical ASAP that incorporates the selection of an appropriate benzodiazepine rescue medication would seem a logical approach to reducing patient morbidity and mortality, reducing family anxiety, and saving health care costs. However, examining the economic impact of rescue medications is more challenging than demonstrating their efficacy. Faught addresses the economic aspects of rescue medications by reviewing multiple types of economic issues to consider (e.g., cost of illness, cost of rescue medication) and types of analyses that may be utilized (e.g., cost-effectiveness, cost-utility, and cost–benefit) related to seizure clusters and their treatment. Despite having incomplete data for many of these analyses, Faught demonstrates key aspects of these analyses and some logical conclusions using basic assumptions from existing clinical trial data. He also discusses both the opportunity and the challenges involved with prospectively conducting economic studies of rescue medications for seizure clusters.

Although seizure cluster clinical trials have addressed important aspects of rescue treatment efficacy, tolerability, and safety, many practical real-world clinical issues have been left unanswered. The strengths of regulatory clinical trials, including their focused purpose, scope, design, and study populations, are also inherent limitations. Great opportunities exist for enhancing the generalizability and impact of future research in rescue treatments. Wheless and an expert panel examine these topics through a narrative review approach. Topics addressed include alternative approaches to clinical trial outcomes, end points, and study populations; potential use of devices to improve treatment development programs; innovative approaches to examine seizure cluster prevention and prediction; alternative study designs; and potential novel investigative paradigms.

The future is brighter for people who experience seizure clusters. Appreciation is growing for the need for personalized seizure cluster definitions rather than a “one-size-fits-all” approach. Effective, well-tolerated, and safe rescue treatment options are available, and there is growing understanding among practitioners, families, and patients about when and how to use them by implementing ASAPs. Current and future research will refine and improve treatment options. The impact of these advances is optimized when health care providers communicate with, listen to, and partner with their patients and caregivers in the shared goal of achieving the best quality of life.

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