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REVIEW ARTICLE

Practical Questions About Rescue Medications for Acute Treatment of Seizure Clusters in Children and Adolescents with Epilepsy in the USA: Expanding Treatment Options to Address Unmet Needs

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Abstract

Epilepsy is a common pediatric neurological condition, affecting approximately 470,000 children in the USA and having a prevalence of 0.9% in the global population of approximately 2.6 billion children. Epilepsy is associated with disruptions in several areas of a child's life, including medical burden, quality of life, cognitive outcomes, and higher risk of mortality. Additionally, some pediatric patients may experience acute seizure emergencies such as seizure clusters (also called acute repetitive seizures), which are intermittent increases in seizure activity that differ from the patient's usual seizure pattern and may occur despite daily antiseizure drug administration. Seizure clusters increase a patient's risk for status epilepticus and emergency room visits. Benzodiazepines are the main category of drugs used as acute seizure therapies for seizure clusters. This narrative review provides a practical discussion of care for pediatric patients with epilepsy and seizure clusters exploring such topics as details about the US Food and Drug Administration-approved acute seizure therapies, safety and ease of use of these medications, benefits of seizure action plans to help ensure optimal treatment, and considerations for transitioning a pediatric patient with acute seizure therapy to adult healthcare management.

Key Points

Pediatric patients with epilepsy who experience acute seizure clusters require prompt treatment to lower the risk of negative outcomes.

Consideration should be given to the unique characteristics associated with each approved acute seizure therapy formulation and route of administration.

Seizure action plans may be beneficial for pediatric management and transitioning to adult healthcare.

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1 Introduction

Patients with epilepsy, including pediatric patients, may experience acute seizure emergencies such as seizure clusters, which can be described as intermittent increases in seizure activity that occur despite administering daily antiseizure medications (ASMs) [1]. Prompt effective treatment of seizure clusters is important to reduce the risk of negative outcomes, with benzodiazepines being integral to acute management [2, 3]. Because seizure clusters commonly occur outside medical facilities, acute treatment requires portable outpatient options that trained caregivers in the community can administer [2].

There is no current consensus regarding a precise definition of seizure clusters, and no definition has been provided in the International League Against Epilepsy classifications [3, 4]. The US Food and Drug Administration (FDA) indication includes "intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern" [5–7]. Clinical definitions of seizure clusters usually include a number of seizures within a certain time period, such as two or more seizures in 24 h, but there have been variations in both criteria (e.g.,

three seizures, 48 h), and such definitions lack insight into a patient's individuality [3, 8]. In addition to the differences in definitions for seizure clusters, there are associated terms including acute repetitive seizures, cluster seizures, and serial seizures.

In Europe and other regions, this type of seizure emergency may be treated as an acute seizure or a type of prolonged acute convulsive seizure [3, 9]. Examples of approved therapies in the European Union include rectal diazepam solution for epileptic convulsions in patients aged ≥ 1 year and buccal midazolam for children and adolescents aged 3 months to < 18 years with prolonged acute convulsive seizures [10, 11].

Although not indicated for acute treatment of seizure clusters, other medications, such as oral benzodiazepines and atomized midazolam for injection, also have been administered in this context. However, in the absence of clinical trial programs, the effectiveness and tolerability of these agents in this application may not be well characterized. Oral medications may be affected by first-pass metabolism and variable gastric emptying, and the intravenous midazolam formulation has a low pH associated with substantial nasal irritation and requires a high volume of administration [2, 12].

This paper focuses on the approved indication of seizure clusters in pediatric patients in the USA and does not examine this type of treatment in the European Union or other areas of the world, which may differ. Although important for global inclusivity, details on treatment in additional global regions are not directly applicable to the scope of this US-centered paper. Additionally, the alignment between prolonged acute convulsive seizures and seizure clusters has not been precisely defined for our target audience.

This narrative review addresses questions related to seizure clusters in pediatric patients with epilepsy and about treatment with acute seizure therapies. The review focuses on content from published manuscripts addressing the current knowledge about pediatric patients with seizure clusters. The PubMed database was searched for recent articles (2000 and later) published in English; articles published early were included as needed (e.g., for medication approved before 2000). The primary search terms, determined by author consensus, included combinations of *acute repetitive seizure, adolescent, benzodiazepine, child, children, epilepsy, nasal spray, pediatrics, rectal, rescue treatment, seizure,* and *seizure cluster*. References from published papers were reviewed for additional relevant sources. Practical questions relevant to pediatric epilepsy syndromes, epilepsy management, and treatment of seizure clusters were distilled from the literature by the authors and discussed here (Table 1).

2 What Are Some of the Consequences of Unmanaged Seizure Clusters?

Unmanaged seizure clusters may have negative outcomes. Patients experiencing a higher seizure frequency are at risk for seizure-related injuries and hospitalizations; administration of acute seizure therapy may reduce this risk [13]. Emergency room visits can be high among persons with untreated seizure clusters because patients are often taken to the emergency room first [1]. Such potentially avoidable use of the emergency room can be disruptive to patient/caregiver daily activities, increase the burden of caregivers, and increase costs associated with epilepsy care [1].

Seizure clusters also can reduce the quality of life of patients with epilepsy and their caregivers by affecting overall mood, ability to work, and personal activities (e.g., social activities and travel) [1]. Acute seizure therapy may help with stabilizing or potentially improving some facets of quality of life [14].

In addition to seizures, uncontrolled epilepsy can be associated with a loss of predictability for patients and caregivers that can result in fear and anxiety associated with concerns about such issues as prognosis, the future, and medication [15]. Anxiety may be associated with avoidance of activities to potentially avoid seizure clusters in a pathological condition that has been called anticipatory anxiety or seizure phobia [16, 17]. Psychiatric comorbidities are common with epilepsy, and clinicians providing care to patients with epilepsy should consider including questions to screen for these conditions among both patients and caregivers during office visits [18–21]. Potential treatment of psychiatric comorbidities should be tailored to the individual and their family. Psychiatric referral should be considered, and treatment is likely to be multidisciplinary, potentially including pharmacotherapy, cognitive behavioral therapy, and patient empowerment with education and use of a seizure action plan.

3 Why Is Prompt Treatment with Acute Seizure Therapy Important?

Prompt treatment is needed to reduce the risks associated with seizure clusters. Trained caregivers are generally able to recognize the onset of seizure clusters as distinct from the child's other seizures in frequency, duration, severity, or type, allowing for the opportunity to address the episode quickly [22]. Delay in treatment may result in injury as well as prolonged seizures that may not be as responsive to acute seizure therapy [23, 24]. Prompt treatment may allow for more rapid seizure cluster cessation and reduce the risk of status epilepticus [22]. Acting to control a seizure cluster

Table 1 Epilepsy rescue medication questions and current answers for pediatric care

Question	Summarized current answer
What are some of the consequences of unmanaged seizure clusters?	Consequences include injury, hospitalization, ER use, reduced quality of life, and fear or anxiety
Why is prompt treatment with acute seizure therapy important?	Prompt treatment has been associated with reduced risks linked to seizure clusters, such as prolonged seizures
Are drugs historically used as daily ASMs also appropriate for acute seizure therapy?	Daily ASM formulations have limitations as acute seizure therapy
What drugs are approved for acute treatment of seizure clusters in pediatric patients and at which ages?	The acute seizure therapies for pediatric patients with seizure clusters are diazepam rectal gel (age ≥2 years), midazolam nasal spray (age ≥12 years), and diazepam nasal spray (age ≥6 years)
What are the pediatric safety profiles of the approved acute seizure therapies?	All three have been shown to have good safety profiles in overall populations of adults and children
Can a pediatric patient be transitioned from an acute seizure therapy with rectal administration to one with intranasal administration?	Patients may be transitioned from rectal to intranasal administration when aged ≥6 or ≥12 years; dosing is similar between diazepam rectal gel and diazepam nasal spray
Are the acute seizure therapies for seizure clusters easy to administer?	Rectal administration has limits that affect ease of use; caregivers have reported that diazepam nasal spray is easy to use
Is a seizure action plan useful for pediatric patients prescribed acute seizure therapies?	Seizure action plans can include the information school nurses and other personnel could use during school hours; an acute seizure action plan can be beneficial during emergency situations
What is the SEIzure cluster interVAL (SEIVAL) between seizure clusters, and how might it change how we think about evaluation of acute seizure therapies?	Examination of the duration in days between treated seizure clusters over time could potentially be used as a metric for effectiveness
What should be considered when transitioning a pediatric patient with acute seizure therapy to adult healthcare management?	Beneficial practices in pediatric management including acute seizure therapy selection and seizure action plan use should be considered when transitioning pediatric patients to adulthood

ASM antiseizure medication, *ER* emergency room

may empower patients to treat first and not immediately seek help from emergency services [1], potentially reducing stress and anxiety.

4 Are Drugs Historically Used as Daily ASMs Also Appropriate for Acute Seizure Therapy?

Selection of the appropriate seizure therapy involves consideration of such factors as the patient's age, seizure type, type of epilepsy, and any comorbid conditions, as well as understanding of the potential treatment-emergent adverse events (TEAEs) associated with the seizure therapy [25, 26]. Ideal ASM treatment would control seizures with limited TEAEs [26]. First-line ASMs for pediatric patients are often provided orally as a tablet, capsule, solution, or suspension [26]. In emergency situations such as seizure clusters, oral administration may have limitations because of the inability to swallow, potential for choking or aspiration, biting risk, and delayed efficacy due to variable gastric absorption and first-pass metabolism [27–29]. There are no oral medications approved for acute treatment of seizure clusters.

Additionally, intravenous midazolam administered intranasally with an atomizer has been used off label for treating acute seizures in pediatric patients [30]. Nasal administration of this type has shortcomings, such as requiring a large volume of 1000 µL (1 mL; five-fold higher than the 200-µL volume of the total nasal cavity) and the low pH (~ 3) being poorly tolerated [2, 31]. Formulations of midazolam and diazepam that were specifically developed for intranasal administration are available and approved by the FDA for acute seizure therapies [6, 7].

5 What Drugs Are Approved for Acute Treatment of Seizure Clusters in Pediatric Patients and at Which Ages?

5.1 Diazepam Rectal Gel

In 1997, diazepam rectal gel was approved by the FDA for acute treatment of seizure clusters in patients aged ≥ 2 years [2, 5]. Administration of the formulation requires caregiver use of a nonsterile, prefilled, unit-dose delivery system with a molded tip [5]. Packaging includes two delivery systems (i.e., two doses) and packets of lubricating jelly. Recommended doses range from 5 to 20 mg based on the patient's

age and weight (i.e., 2–5 years, 0.5 mg/kg; 6–11 years, 0.3 mg/kg; and ≥ 12 years, 0.2 mg/kg). If part of the first dose is expelled, a 2.5-mg dose is also available [5]. Before administration, the patient should be placed on their side facing the caregiver; the device removed from package, prepared, and the tip lubricated; and clothing removed as needed for access to the rectum (Fig. 1). Once administered, instructions include steps to minimize leakage. If prescribed, a second dose can be provided 4–12 h after the initial dose to control seizure cluster recurrence [5].

5.1.1 Pediatric Efficacy Results

Data from two prospective, placebo-controlled studies were combined in an analysis of the results from patients aged 2–17 years who completed treatment with diazepam rectal gel for seizure clusters [32]. Efficacy was assessed based on seizure frequency, caregiver's evaluation of outcome, and time to next seizure. A total of 68 patients treated with diazepam rectal gel and 65 given placebo were included in the analysis. The differences in seizure frequency (i.e., reduction) and time to next seizure (i.e., lengthening) between the diazepam rectal gel and placebo groups were significantly better in the diazepam rectal gel group ($P < 0.001$ for both). Caregivers' global evaluation of outcome compared with prior episodes significantly improved with diazepam rectal gel administration in one of the studies ($P < 0.001$) but not in the other ($P = 0.053$) [32, 33].

5.2 Nasal Sprays

Midazolam nasal spray and diazepam nasal spray were approved by the FDA in 2019 and 2020, respectively, for acute treatment of seizure clusters in patients with epilepsy [2, 6, 7]. Although these nasal sprays use a similar device for administration, each formulation has unique characteristics.

5.2.1 Midazolam Nasal Spray

Midazolam nasal spray is approved for use in patients aged ≥ 12 years [7]. Midazolam nasal spray is provided as a solution in a single-dose delivery device. The packaging includes two nasal delivery devices in individual blister packs. Each dose is 5 mg in 100 µL of solution, which is the full dose regardless of patient age or weight. Before administration, the blister packaging should be opened and the device removed and held appropriately in one hand; the device should not be primed nor should the plunger be pressed before placement in the patient's nose (Fig. 1). If there is no response from the initial dose and a physician has instructed use of a second dose, it can be administered into the other nostril after 10 min [7].

Midazolam nasal spray is highly concentrated and aqueous [2]. This formulation has a clear colorless-to-yellowish appearance and includes organic solvents for increased solubility with pH maintained at 5–9 [2, 7].

5.2.1.1 Midazolam Nasal Spray Pediatric Efficacy Results

In the randomized, double-blind, placebo-controlled trial evaluating midazolam nasal spray in 292 patients with seizure clusters, 18 patients were aged 12–17 years, and five were randomized to active treatment [34]. The primary efficacy outcome was based on treatment success defined as termination of seizures within 10 min of administration with no recurrence up to 6 h. In the overall population (adults and children), a statistically significant and clinically meaningful treatment effect was shown, with a difference of 19.4% between the midazolam nasal spray group and the placebo group ($P = 0.01$). Across all age groups in the extension trial

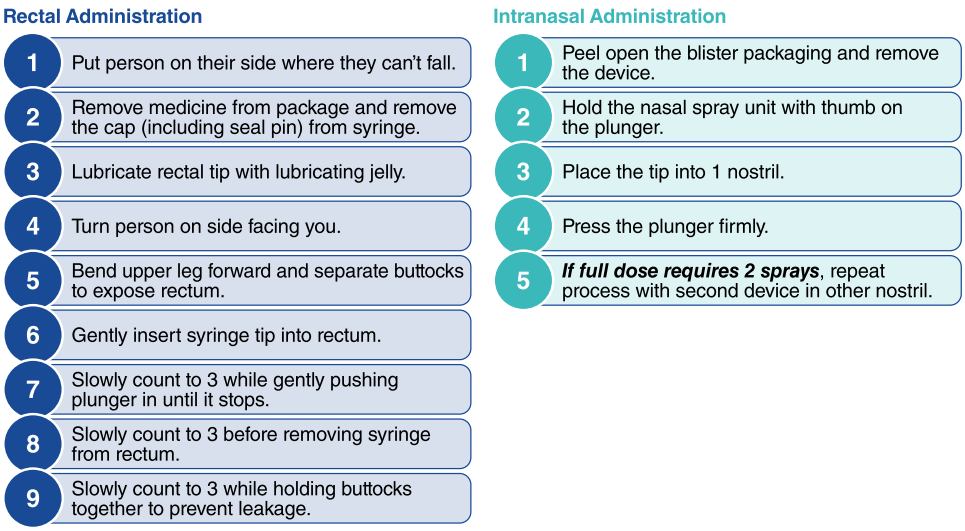

Fig. 1 Steps for rectal and intranasal administration of US Food and Drug Administration-approved acute seizure therapies [5–7]

($N = 161$), 38.5% (769/1998) of seizure clusters had second doses administered within 6 h of the first dose, suggesting effectiveness of single doses [35]. Efficacy was not specifically reported for the subgroup of pediatric patients [34, 35].

5.2.2 Diazepam Nasal Spray

Diazepam nasal spray is approved for use in patients aged ≥ 6 years [6]. Diazepam nasal spray is provided in single-dose delivery devices prefilled with solution at 5-, 7.5-, or 10-mg strength for doses of 5, 10, 15, or 20 mg. Each blister pack contains a full dose, with the 5- and 10-mg packages including two blister packs, each pack with one delivery device. The 15- and 20-mg packages contain two blister packs, each with two delivery devices to provide the full dose (i.e., two 7.5-mg devices for the 15-mg dose and two 10-mg devices for the 20-mg dose). Recommended doses are based on the patient's age and weight (i.e., 6–11 years, 0.3 mg/kg and ≥ 12 years, 0.2 mg/kg) [6]. Before administration of the 5- and 10-mg doses requiring one delivery device, the blister pack should be opened and the device removed [36]. The device should be held with the index and middle fingers on either side of the nozzle with the thumb on the plunger. The plunger should not be pushed until the device is placed in the patient's nose, with the index and middle finger touching the bottom of the nose. For the 15- and 20-mg doses, use of two delivery devices is required for the full dose [36].

Included in the diazepam nasal spray formulation is dodecyl maltoside, an alkylsaccharide absorption enhancer, and vitamin E as a nonaqueous solvent [2, 6]. Diazepam nasal spray has a clear pale amber appearance [6].

5.2.2.1 Diazepam Nasal Spray Pediatric Effectiveness Results In the open-label repeat-dose safety study evaluating diazepam nasal spray as acute treatment for seizure clusters ($N = 163$), 45 patients were aged 6–11 years and 33 were aged 12–17 years [37]. A proxy for effectiveness in the study was the proportion of second doses used within 24 h of the initial dose (with 12.6% for the overall safety population) [38]. A sub-analysis of pediatric patients demonstrated that among patients aged 6–11 years, second doses were used for 11.5% of seizure clusters; among those aged 12–17 years, second doses were used for 11.3% of seizure clusters [37]. These data suggest effectiveness with a single dose of diazepam nasal spray administered to pediatric patients [37]. Diazepam nasal spray is currently being evaluated in other regulatory regions, including the Asia-Pacific region [39].

There is currently no acute antiseizure therapy alternative to diazepam rectal gel in patients aged < 6 years, and there are no pharmacokinetics data for diazepam rectal gel in this age group. To explore this gap, an open-label safety study was undertaken to evaluate the pharmacokinetics of diazepam nasal spray in patients aged 2–5 years [40]. Included in this study were patients in this age group who had epilepsy and seizure clusters and who had been administered rescue medications at least once per month in the 3 months before joining the study. The initial pharmacokinetic profile and repeated-dose safety of diazepam nasal spray in this age group [40] are being analyzed for regulatory submission.

6 What Are the Pediatric Safety Profiles of the Approved Acute Seizure Therapies?

All three seizure therapies approved for use for seizure clusters carry class warnings about risks with concomitant use of opioids and central nervous system depressants [5–7]. In clinical trials, all three have been shown to have favorable safety profiles in overall populations of adults and children. In the diazepam rectal gel pediatric analysis, the few adverse events were deemed to not have clinical importance [32]. There were no reports of serious respiratory depression. Somnolence was the only adverse event with a significantly higher rate in the treated group than in the placebo group (25% vs 7.7%, $P = 0.01$) [32]. In the midazolam nasal spray placebo-controlled study, a specific pediatric safety analysis was not conducted; however, per the authors, the safety profile was favorable in the overall population of adults and children [34]. Most TEAEs were considered of mild or moderate intensity. Incidence of respiratory depression was < 1% and only occurred in the test phase of the trial [34]. For patients at risk of respiratory depression, administration under the supervision of a healthcare professional should be considered [7]. In both the test and comparative phases, nasal discomfort was the most common TEAE (5.5–16.3% in patients treated with one or two doses vs 7.7% for those receiving placebo only) [34]. Somnolence was more common in treated patients than in those receiving placebo (9.3–9.9% vs 3.8%, respectively) [34]. In the open-label extension study, treatment-related TEAEs occurred in 35.4% of patients [35]. In the diazepam nasal spray open-label safety study, rates of TEAEs in the pediatric age groups were similar (6–11 years, 91.1%; 12–17 years, 81.8%) [37]. Nasal discomfort was not common; aside from seizure, the most common TEAEs were nasopharyngitis in patients aged 6–11 years (26.7%) and pneumonia, pyrexia, somnolence, and upper respiratory tract infection in patients aged 12–17 years (12.1% each). In the full pediatric subgroup, the most common treatment-related TEAEs were epistaxis and somnolence (2.6% each). Across all pediatric patients who received concomitant clobazam and administered diazepam nasal spray, rates of TEAEs and serious TEAEs were similar to those seen in

patients in the overall pediatric subgroups. Incidence of somnolence in patients aged 6–11 years was 6.7%. There were no reports of respiratory depression in the study [37].

7 Can a Pediatric Patient Be Transitioned from an Acute Seizure Therapy with Rectal Administration to One with Intranasal Administration?

Although diazepam rectal gel has been shown to be efficacious, there are some limitations to its use. Administration may be uncomfortable for the patient and socially awkward for the patient and/or caregiver [30, 41, 42], and the National Association of School Nurses recommends using the least invasive route of administration [43]. In addition, rectal administration may not be preferred by adolescent patients [42].

The newer nasal spray formulations are an alternative to the rectal route of administration; there are differences between the two formulations in this context. Patients aged ≥ 6 years could be transitioned from diazepam rectal gel to diazepam nasal spray, which has the same active ingredient as diazepam rectal gel and has been shown to have comparable bioavailability [2] and less variability in bioavailability [44]. Identical age- and weight-based strategies are used for dosing diazepam rectal gel and diazepam nasal spray [5, 6]. Evaluation of midazolam nasal spray for approval was based on a comparison with placebo, but it was not compared with diazepam rectal gel [34]. Midazolam nasal spray is for those aged ≥ 12 years and uses the same dose for all patients regardless of age and weight [7].

8 Are the Acute Seizure Therapies for Seizure Clusters Easy to Administer?

At the time of its approval, diazepam rectal gel was the first option for administration by nonmedical caregivers [45]. In the overall population of one of the open-label studies of diazepam rectal gel, caregivers reported high satisfaction with treatment, despite difficulties with administration such as their own anxiety, patient discomfort, and patient privacy concerns [46]. Rectal administration requires many steps, including positioning and undressing the patient [5, 42], which may be difficult to do for some patients (e.g., larger patients or those in wheelchairs) and may delay administration. Studies of ease of administration of midazolam nasal spray are not available, but studies have compared the use of diazepam rectal gel and atomized intranasal midazolam. In a study of caregiver preference for diazepam rectal gel or atomized midazolam for pediatric patients, significantly more caregivers felt that atomized midazolam was easier to use ($P = 0.0038$) and that they felt more comfortable with its administration ($P = 0.0004$) [47]. In another study, caregivers of pediatric patients with a prescribed rescue therapy reported greater ease of administration and greater overall satisfaction for atomized midazolam compared with diazepam rectal gel [30]. For diazepam nasal spray, more than half (54.3%) of caregivers of pediatric (73.8%) and adult (26.2%) patients responding to a survey rated administration of diazepam nasal spray as extremely easy and more than a third rated it as very easy (39.5%) [48]. Two pediatric patients (as young as 11 years of age) reported self-administration on the survey [48]. Regarding prior use of diazepam rectal gel, the majority of caregivers (64.3%) rated rectal administration not at all easy compared with diazepam nasal spray [48]. The FDA has stated that the intranasal route of administration of diazepam nasal spray provides significantly improved ease of use over rectal administration [49].

9 Is a Seizure Action Plan (SAP) Useful for Pediatric Patients Prescribed Acute Seizure Therapies?

A seizure action plan (SAP) could be beneficial as part of a pediatric patient's epilepsy management and is required by many school districts [50]. Seizure action plans are integral to Seizure Safe Schools legislation, which is supported by the Epilepsy Foundation and modeled on the advocacy work of Epilepsy Teens Speak Up! Ambassador Lyndsey Crunk in collaboration with the Epilepsy Foundation of Kentuckiana for the passage of the first state law on this topic in Kentucky [51, 52]. The National Association of School Nurses has recommended that children with seizures have an SAP as part of an individualized healthcare plan [43]. In the school environment, school nurses need to know the physician's medical orders for a pediatric patient with epilepsy to confidently provide care if needed during school hours [53]. School personnel also need to know if a child should stay in school following a seizure or needs care at a medical facility. This type of information can be provided clearly in an SAP for school nurses or other school personnel [53]. Additional information in an SAP include details about the pediatric patient's medications and seizure type [41].

Additionally, an acute SAP—a version of the SAP that is individualized, brief, and easy to follow during an emergency—can provide concise information about when and how to administer acute seizure therapies as the patient's physician has instructed [50]. Having such an acute SAP readily available may help empower patients and caregivers (including infrequent caregivers such as babysitters and

grandparents) and reduce fear and unnecessary healthcare utilization [50].

10 What Is the SEIzure interVAL (SEIVAL) Between Seizure Clusters, and How Might It Change How We Think About Evaluation of Acute Seizure Therapies?

The SEIzure interVAL (SEIVAL), the duration in days between treatments for seizure clusters, was examined over time in a novel analysis of adult and pediatric patients treated with a diazepam nasal spray as a potential metric of effectiveness for acute seizure therapies [54]. SEIVAL was looked at in 90-day periods, and patients with one or more SEIVAL (i.e., at least two seizure clusters) in each of the first four periods (up to 360 days) made up a consistent cohort, which was designed to minimize retention bias. Second doses that were given as re-treatment for a single cluster were not included in the analysis. In the pediatric subgroup ($n = 32$; aged 6–17 years), mean SEIVAL significantly increased from 13.0 days at Period 1 (1–90 days) to 25.9 days at Period 4 (271–360 days; $P = 0.02$) [54]. This reduced use of therapy over time supports the evidence of a lack of tolerance that was previously shown with diazepam nasal spray [55]. Further investigation into hypotheses regarding the cause of the increase (e.g., biological factors, behavioral reasons, and regression to the mean) and application of the SEIVAL metric has been suggested [54].

11 What Should Be Considered When Transitioning a Pediatric Patient with Acute Seizure Therapy to Adult Healthcare Management?

In many cases of transitioning adolescents with epilepsy to adult healthcare management, a generic transition program with epilepsy-related materials may be provided beginning at ages 12–14 years [56]. Use of acute seizure therapies that are easy to administer and are seen as socially acceptable during pediatric management may contribute to better adherence during adulthood [37]. Similarly, development and use of an SAP during pediatric management may help continue SAP use in patients transitioning to adult care; it has been shown that fewer adults than pediatric patients have an SAP [57]. Pediatric patients moving on to adult care (including patients going to college) would also benefit from current diagnostic information, up-to-date treatment and emergency plans, and documentation of any comorbidities [56].

12 Conclusions

Pediatric patients may develop epileptic syndromes that include intractable seizures and seizure emergencies such as seizure clusters. Physicians treating these patients should be aware of the unique details associated with each approved acute seizure therapy formulation and route of administration, caregiver perceptions regarding administration, and the importance of an SAP for pediatric management and transitioning to adult healthcare management.

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