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This ACADEMIC HIGHLIGHTS section of *The Primary Care Companion for CNS Disorders* presents the highlights of the teleconference series “Today’s Options in Epileptic Seizure Rescue Treatment,” which was held in April and August 2021. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by educational grants from UCB, Inc., and Neurelis, Inc.

The teleconference was chaired by **Kamil Detyniecki, MD**, University of Miami, Florida. The faculty member was **Patricia Penovich, MD**, Minnesota Epilepsy Group, St. Paul.

CME Objectives

After studying this article, you should be able to:

- Educate patients who are at risk for seizure clusters about rescue medications and emergency plans
- Provide rescue treatment for seizure clusters that patients and their caregivers will use

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New Options for Rescue Treatment in Individuals With Epilepsy Seizure Clusters

Kamil Detyniecki, MD, and Patricia Penovich, MD

Many patients with epilepsy experience “clusters” of seizures.¹ Seizure clustering has a significant impact on patients’ emotional well-being, daily function, productivity, and quality of life and is associated with increased use of emergency departments.¹

This report, based on presentations given by Kamil Detyniecki, MD, and Patricia Penovich, MD, will address how to educate patients who are at risk for seizure clusters about rescue medications and emergency plans and how to provide rescue treatment that patients and their care partners will use.

DEFINITION, EPIDEMIOLOGY, AND IMPACT OF SEIZURE CLUSTERS

Definition

Dr Penovich began her presentation by describing the challenges presented by the lack of consensus on the definition of seizure clusters. Multiple terminologies have been used over the years to describe the same clinical phenomenon, including *acute repetitive seizures*, *flurries*, and *cyclical, serial, repetitive, crescendo, and recurrent seizures*.² In fact, *seizure cluster* is not listed in the International League Against Epilepsy (ILAE) Commission on Classification and Terminology, nor is there a billing code that recognizes this clinical phenomenon. She emphasized the need for a common language around seizure clusters, as variable definitions have been used in the methodologies of different studies (eg, number of seizures, time period, change in pattern of seizure clusters). An accepted definition would enable the provision of clear direction as to when rescue treatment may be needed.³ A recent review² described clusters as series of grouped seizures that have short interictal periods. They may occur with any seizure type, ranging from focal seizures with or without maintained awareness and/or motor expression to generalized seizures with or without motor expression. Clusters do not include status epilepticus.

Epidemiology

Dr Penovich cited a diary study⁴ by Fisher et al that found that, in a population of 5,098 community outpatients, 1,177 (23%) had multiple seizures in a 24-hour period. One-fourth of days with any seizures included clusters. One-third of seizures occurred within 3 hours of the initial event and two-thirds occurred within 6 hours. When more than 2 seizures occurred, the time to the next seizure decreased from an average of over 2 hours (to the third event) to 15 minutes (from the fourth

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Dr Detyniecki has received honoraria from Neurelis, UCB, Greenwich, and Aquestive. Dr Penovich is a consultant for LVIS, Neurelis, Engage, SK-Pharma, and UCB and is a member of the speakers/advisory boards for Greenwich, Neurelis, and SK-Pharma.

Review Process

The faculty member(s) agreed to provide a balanced and evidence-based presentation and discussed the topic(s) and CME objective(s) during the planning sessions. The faculty's submitted content was validated by CME Institute staff, and the activity was evaluated for accuracy, use of evidence, and fair balance by the Chair and a peer reviewer who is without conflict of interest.

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to the fifth event). Another study⁵ in patients using free text notes in an electronic seizure diary found that 24% of patients had seizure clusters. The median number of seizure cluster days per year was 13.7, and the median number of seizures in a cluster day was 3. The mean number of seizures in a cluster day was 4.

Dr Penovich described "triggers" or periods of vulnerability to seizure clusters.² Patients and care partners may recognize triggers such as sleep deprivation, stress, missed medication doses or changes in medication, illness with fever, use of alcohol or other nonmedical drugs, and hormonal changes; conversely, some people have no identifiable trigger.⁶



Family Perspectives

Here, a spouse describes the development of her husband's seizure clusters:

"My husband was diagnosed with epilepsy when he was 6. He had very infrequent seizures (maybe 1–2 a year); medication controlled them completely, and his doctors were confident he would outgrow them. As a teenager, he would often skip doses for months at a time with no issues. As an adult, he would rarely miss any, but within the last few years (he is 34) his seizures became more frequent. He was on [medication] but had breakthrough seizures; he was having at least one episode a month, with each episode containing 2–3 seizures about 30–45 min apart. He has been switched to [different medication], which seems to work, but if he misses even a single dose, he is pretty much guaranteed to have a seizure."⁷

Impact

Patients experience a range of consequences of seizure clusters. A study⁸ found a greater risk of status epilepticus in patients with seizure clusters (44.0%) than in those without (12.5%). Other possible consequences that patients with seizure clusters face include increased use of emergency services,⁹ greater financial burden,¹⁰ higher rates of hospitalization,¹¹ higher rates of postictal psychosis,¹² and decreased quality of life.⁹ Both patients and their care partners are affected by the occurrence of seizure clusters and have noted having elevated fear and anxiety and a hesitancy to travel away from home.⁹



Patient Perspectives

Here, a patient notes the impact of a seizure cluster:

"[It] leaves me exhausted, depressed, needing a day off from work."¹³

A patient who was diagnosed with epilepsy in midlife describes the impact of the disease on her life:

"Being new to all of this is somewhat scary. I have some knowledge of [seizures] due to friends of the past having epilepsy. With that said, it's all a new ballgame for me. I'm finding for the first time in my life that my favorite pastime is not available (driving)... I'm concerned that life is going to get harder."¹⁴

This patient is worried about the increasing frequency of seizures:

"I have noticed the time between when I have episodes getting shorter. My first one ... was followed by a second one an hour after the first. I then went 6 years off meds and had another at home before work, which was followed by another an hour or so later. I went a year off meds and had nothing till about 2 months ago. I felt off, called family, and had another one, followed by 2 more the same day. I'm now on [medication]. Made it 2 months and just had another grand mal this past weekend, but only one. I don't know what to do; I feel like a burden on my family."¹¹

Communication

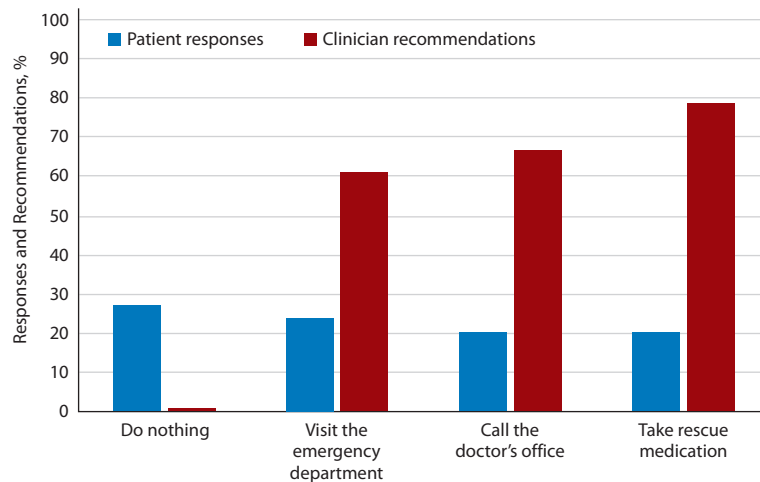
Dr Penovich discussed the differing perspectives of patients with epilepsy, their caregivers, and health care professionals.¹³ Communication about seizure clusters is impeded not only by the lack of an accepted definition but also by the varying experiences of patients. While patients know that clusters differ from their usual seizure events, they find them difficult to describe to clinicians. Practitioners should consistently ask patients about changes in seizure pattern, encourage patients to keep a seizure diary, and ask about the impact of clusters.

Dr Penovich described the Seizure Cluster Burden of Illness US Survey,⁹ which was conducted on behalf of The Epilepsy Foundation. The survey queried patients aged 18 years and older with epilepsy or a seizure disorder who had experienced seizure clusters in the past year, caregivers providing current care for a patient

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Figure 1. Patients' Responses to Seizure Clusters Versus Clinicians' Recommendations



Data from Penovich et al.⁹

with seizure clusters (adult or child), and neurologists or epilepsy specialists who treat adult or pediatric patients. Discrepancies were found in the perceived degree of negative impact of seizure clusters between the patients/caregivers and the clinicians. However, although patients and care partners assigned a greater burden to clusters than did the physicians, their actions to address clusters often did not align with the recommendations made by the clinicians in the survey (Figure 1).⁹



Family Perspectives

Being a caregiver of a child with epilepsy presents a host of challenges across many areas of daily life. Here, parents share their feelings of concern:

"He's out of it for the day... [it] bothers me because it's like he lost a day of his life."¹³

"My 11-year-old son was diagnosed in January. How do the parents cope with this? I am in constant fear & stress over my child's safety. I constantly question 'is he about to have a seizure?' Every time he goes to take a shower, or use the bathroom, even though I am nearby, I am terrified. I am terrified any time he is alone for any short period of time... I have dealt with so many extremely difficult challenges in my life, but having an issue like this happen to my child is the most incredibly difficult obstacle I have ever faced. I don't know how to handle this stress."¹⁵

Action Plans

Dr Penovich reported that the Seizure Cluster Burden of Illness US Survey⁹ found that only 30% of patients reported having a seizure emergency plan. However, 75% of patients somewhat or strongly agreed that they live in fear of having a seizure at any time. These statistics highlight an area in which clinicians can help patients. To provide a sense of control that could lessen patients'

fear, Dr Penovich identified 2 important tools: Seizure Action Plans (SAPs)¹⁶ and Acute Seizure Action Plans (ASAPs).¹⁷ The SAP is "an abbreviated medical record" that the patient and their caregivers can use at home, work, and school. The plan is individualized according to each patient's particular circumstances. The ASAP can be part of the longer SAP, or it could be separated into a stand-alone document. The ASAP should be clear, concise, and easy to use and should be updated when patients' medications are changed or the dose is adjusted by weight. The ASAP should describe the steps to take, the rescue medication to be used, and when to call for emergency aid.

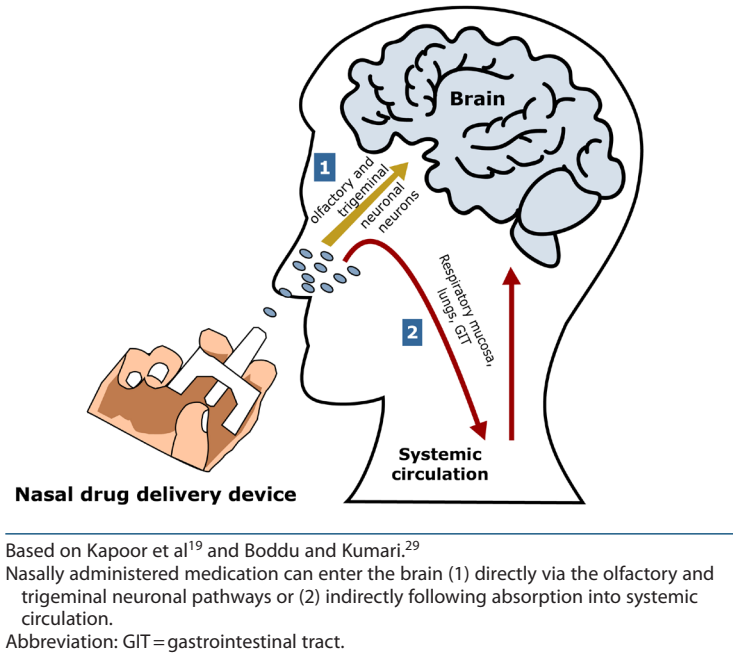
THERAPEUTIC ADVANCES FOR EPILEPTIC SEIZURE RESCUE

Dr Detyniecki outlined the characteristics of an ideal rescue therapy for treatment of seizure clusters: a broad spectrum of efficacy, rapid cessation of seizures (ie, within minutes), ease of use requiring minimal patient cooperation, safety and minimal discomfort, low inter- and inpatient variability, adult and pediatric doses/delivery systems, and long shelf life.¹⁸ When developing a rescue treatment plan, the clinician should describe all available treatment options and should individualize care to the patient's circumstances (such as times of traveling, high stress, or lost sleep).³

Rescue Medications

Treatment of epileptic seizure emergencies requires rapid delivery of antiepileptics such as benzodiazepines to the brain.¹⁹ Dr Detyniecki reported on the rescue medications that are currently available and in the pipeline for the acute treatment of seizure clusters. Current medications include intranasal midazolam,²⁰ intranasal diazepam,²¹ rectal diazepam,²² and buccal midazolam

Figure 2. Direct and Indirect Intranasal Drug Delivery Pathways



(approved for use in Europe).²³ Medications in the pipeline include diazepam buccal soluble film,²⁴ intrapulmonary alprazolam,²⁵ and diazepam autoinjector.²⁶

Rectal diazepam. Dr Detyniecki discussed the advantages and disadvantages of rectal diazepam.²² The advantages include the following:

- it does not require refrigeration
- the syringes are prefilled
- familiarity with the product
- lack of need for patient cooperation (eg, swallowing oral medication).

The disadvantages include the following^{27,28}:

- patients’ fear and embarrassment because of the medication delivery system
- slower administration compared with other formulations
- variable absorption because the drug may be expelled during the seizure
- self-administration is unlikely.

Intranasal formulations. Dr Detyniecki presented an overview of intranasal rescue drugs. Intranasal delivery offers direct and indirect pathways to the brain (Figure 2).^{19,29} The nasal route is attractive for several reasons: its noninvasiveness and social acceptance, rapid onset of action, high vascularity and relatively large absorptive surface area of the nasal cavity, and avoidance of metabolism through the intestines and liver.¹⁹ Disadvantages include restricted dosing volume, anterior leakage and posterior drainage, and variable nasal

absorption in the presence of conditions such as allergies, the common cold, and polyps.



Patient Perspectives

Here, a patient with seizure clusters acknowledges the need for rescue treatment:

“Clusters are the worst...rapidly repeating shocks, disrupted thoughts/confusion and involuntary head nodding...they require intervention to stop, so I have a rescue medication.”¹³

Another patient living with epilepsy for nearly 30 years discusses the positive role that treatment has played in the management of his illness:

“Now I am pretty well controlled – most people don’t even know I have epilepsy... My doctor wants me to reduce my medication, but I don’t want to lose control and I don’t want anyone to know I have seizures.”³⁰

Midazolam nasal spray. Midazolam nasal spray was approved by the US Food and Drug Administration (FDA) in 2019 for the acute treatment of seizure clusters in patients with epilepsy aged 12 years and older.³¹ Dr Detyniecki outlined the dosage and administration information; the dosage is not based on age or weight. Initial use is administered as one 5-mg dose into one nostril.²⁰ He explained that, if the patient has not responded after 10 minutes, an additional spray (5 mg dose) may be administered into the opposite nostril. No more than 2 doses of midazolam nasal spray may be used to treat a seizure cluster. Dr Detyniecki also pointed out that this is not a daily medication, and it is recommended

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Table 1. Midazolam and Diazepam Nasal Sprays for Acute Treatment of Seizure Clusters

	Midazolam Nasal Spray	Diazepam Nasal Spray
Approved age group	12 years and older	6 years and older
Dose based on age/weight	no	yes
Time to second dose	After 10 mins	After 4 hrs
Time to peak plasma concentration (T max) ^a	~15 mins	~1.5 hrs
Time to elimination (half-life)	Up to 6 hrs	~50 hrs
Frequency of use	No more than 2 doses per episode; No more than 1 episode every 3 days; No more than 5 episodes per month	No more than 2 doses per episode; No more than 1 episode every 5 days; No more than 5 episodes per month

Data from VALTOCO package insert²¹ and NAYZILAM package insert²⁰^aT max does not equal time to onset of action.

that intranasal midazolam be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.²⁰

ARTEMIS-1, a randomized, double-blind, placebo-controlled trial³² conducted by Detyniecki and colleagues, evaluated the safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters. A significantly greater proportion of patients achieved treatment success with intranasal midazolam than with placebo (53.7% vs 34.4%, $P = .0109$). Time-to-next-seizure analysis showed early separation (within 30 minutes) between midazolam and placebo that was maintained throughout the 24-hour observation period ($P = .0124$). Dr Detyniecki explained that, during treatment, no patient experienced acute central respiratory depression, and none discontinued due to adverse events.

A post hoc analysis of the ARTEMIS-2,³³ a Phase 3 open-label extension of ARTEMIS-1, assessed patients' treatment satisfaction, anxiety level, and confidence about traveling with midazolam nasal spray. This analysis found that over time patients showed improvements compared to baseline in perceived effectiveness, side effects, convenience, and global satisfaction. Improvement in anxiety and consistently high confidence about traveling with intranasal midazolam were also reported.³³ Additionally, most patients in the trial returned to full baseline functionality after 24 hours. An additional analysis of this study³⁴ showed that 30% of patients were estimated to return to full baseline functionality within 30 minutes and almost 50% within 1 hour.

Diazepam nasal spray. Intranasal diazepam was approved by the FDA in 2020 for the acute treatment of seizure clusters in patients with epilepsy aged 6 years and older.^{21,35} Unlike midazolam nasal spray, diazepam nasal spray dosage is dependent on the patient's age and weight.²¹ Dr Detyniecki discussed the dosage and administration instructions, noting that the initial 5 mg and 10 mg doses are administered as a single spray into one nostril. Administration of 15 mg and 20 mg doses requires 2 nasal spray devices, 1 spray into each nostril. A second dose, when required, may be administered at least

4 hours after the initial dose. Dr Detyniecki added that no more than 2 doses should be used to treat a single episode, and intranasal diazepam is recommended for no more than 1 episode every 5 days and no more than 5 episodes per month.

Dr Detyniecki noted that although midazolam nasal spray and diazepam nasal spray are both benzodiazepines that use the same delivery system, their pharmacokinetics cause them to be dosed differently. See Table 1^{20,21} for a comparison of characteristics of the 2 medications.

Side effects for both midazolam and diazepam nasal sprays are similar; the most common include sedation, headache, and nasal irritation.^{20,21} According to Dr Detyniecki, the acute use of benzodiazepines increases risk for respiratory depression, particularly if the patient uses other central nervous system (CNS) depressants such as opioids. For patients at increased risk of respiratory depression, administration of these products under health care supervision should be considered before initiating treatment at home. Given that both nasal rescue medications are CNS depressants, there is also a potential risk of abuse and addiction.



Patient Perspectives

Here, a patient who experiences cluster seizures explains his overall approach to managing them:

"I am on 3 medications to control my seizures. Stress brings on seizures but exercising daily, sleeping, and eating a balanced diet has helped me. Each person has an individual cause. Now medications have them better under control. The doctor has to know your case a little bit."³⁶

How to Choose the Best Rescue Medication

Dr Detyniecki concluded his presentation with an overview of how clinicians should choose the best rescue medication. Because of differing definitions, doses, and outcome measures, it is difficult to compare the results between studies of different benzodiazepines and delivery methods. He stated that, as long as the medication gets to the brain quickly, the choice of rescue therapy may rely on ease of use and duration of action. Many survey studies have shown that patients and caregivers prefer nasal

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administration over rectal administration.^{17,27,37} (To view the faculty presentations, see the activity “Epilepsy Seizure Clusters: Therapeutic Advances and Emergency Plans” in this CME series at CMEInstitute.com.)



Case Practice Questions

Discussion of the best responses follows the Clinical Points.

Case 1. Jack, a 6-year-old boy with Lennox-Gastaut syndrome, has mild cognitive deficit and attention-deficit/hyperactivity disorder. His epilepsy is characterized by tonic seizures, which occur 2–4 times per month. He has flurries of multiple seizures when he is ill. Jack has a vagus nerve stimulator and takes valproate and oxcarbazepine, and for the flurries he receives rectal diazepam. The latter medication is successful approximately 75% of the time due to problems with administration. Jack is starting a new after-school program that has never had a child with epilepsy. His parents are anxious and fearful about the care he will receive. Which of the following would *not* be a good strategy for this patient and his caregivers?

- Ask the Epilepsy Foundation to arrange a Seizure Smart School Education presentation for the school and after-school program.
- Suggest a trial of nasal diazepam for seizure cluster rescue.
- Develop a Seizure Action Plan and Acute Seizure Action Plan that everyone can access.
- Refer the family to a pediatric epilepsy caregivers support group.
- Ask the school to call 911 each time Jack has a seizure as the school has no experience with children with epilepsy.

Case 2. Michelle, a 28-year-old woman, is planning to travel with friends across Europe and is leaving in 60 days. She has focal epilepsy due to multifocal areas of polymicrogyria. Michelle’s focal seizures are controlled by taking lacosamide 400 mg/d and levetiracetam 750 mg/d. During periods of disrupted sleep or if she is nonadherent to her medications, she may have 3–4 seizures over 4–8 hours. Michelle has had no seizures for the past 6 months and wants advice about her planned travel. What should you advise her to do?

- Do not travel until she has been seizure-free for 1 year.
- Take an extra 400 mg of lacosamide and 750 mg of levetiracetam prior to the flights.
- Use a rescue plan for nasal medication to be administered for a seizure cluster.
- Have a vagus nerve stimulator implanted prior to her travels.

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Disclosure of off-label usage: The faculty members have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents or device therapies that is outside US Food and Drug Administration–approved labeling has been presented in this activity.



Clinical Points

- Cluster seizures are common, and clinicians should ask patients if they have frequent seizure activity that is unlike their usual seizure patterns.
- Only one-third of patients have a seizure emergency plan, and they report often taking different actions than the clinician recommends.
- Developing and using an acute seizure action plan benefits the patient, caregiver, and the health care system.
- Clinicians should choose the best rescue therapy for each patient based on ease of use, speed and duration of action, and patient circumstances.



Discussion of Case Practice Questions

Case 1: Preferred response is **e. Ask the school to call 911 each time Jack has a seizure as the school has no experience with children with epilepsy.**

Twelve local Epilepsy Foundation chapters across the US, as well as a program through the national Epilepsy Foundation, offer training and support to school personnel.^{38,39} Intranasal diazepam is FDA-approved for age 6 years and above. The SAP and ASAP provide a quick summary of the patient’s history, his seizures, his medication, and appropriate emergency and rescue procedures. Parents and siblings are affected by a child with epilepsy. They may be afraid, may experience anxiety or depression as well as lost productivity and financial stresses, and may limit family activities. Support in group settings with a moderator who is knowledgeable in epilepsy may provide families with a more open sharing opportunity than what occurs in the clinician’s office and help improve their coping and quality of life. An ASAP should have information on when to call 911. Although there are situations when an ambulance needs to be called, most seizures do not require emergency medical services.

Case 2: Preferred response is **c. Use a rescue plan for nasal medication to be administered for a seizure cluster.**

There is no guarantee that a seizure will not happen during Michelle’s vacation, which will probably involve episodes of disrupted sleep with transatlantic travel. It is often difficult to maintain a consistent medication schedule across changing time zones, producing instances of medication overuse. Although taking a bolus of her antiseizure medications before flying may be helpful in temporarily increasing her drug levels, it may also produce toxicity. An acute seizure action plan for Michelle and her travel partners will guide prompt, appropriate use of a rescue medication, and nasal formulations can be delivered quickly and without social disruption. Efficacy and tolerability for both intranasal midazolam and intranasal diazepam suggest that either one will permit them to have confidence that the trip may continue without a major medical disruption. Vagus nerve stimulation implantation is approved for refractory epilepsy. It may be a tool that Michelle would consider in the future; however, the efficacy takes some time to be established.⁴⁰

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For the CME Posttest, see next page.



POSTTEST

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1. Patients who experience seizure clusters are more likely to:

- a. Be elderly
- b. Have generalized epilepsy
- c. Have increased anxiety
- d. Have a brain lesion

2. Simon, a 10-year-old boy with epilepsy, has experienced cluster seizures for the past year. He was prescribed rectal diazepam which his mother administers as a rescue medication when necessary. Simon is embarrassed by the medication's delivery system and so you recommend to his mother that he be switched to an intranasal formulation. What common side effect of nasal midazolam or nasal diazepam should you make them aware of before he begins using the new formulation?

- a. Hypotension
- b. Respiratory depression
- c. Rash
- d. Sedation

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