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Epilepsy (E Waterhouse, Section Editor)

Rescue Medications for Acute Repetitive Seizures

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Abstract

Purpose of review This article reviews the current evidence-based treatments for the management of acute repetitive seizures (ARS).
Recent findings Half of patients with refractory epilepsy will experience ARS, but rescue medications are underutilized. Benzodiazepines remain first-line treatment for the management of acute seizures. There are multiple approved medications, and ongoing studies investigating new routes of administration.
Summary Clinicians must recognize patients at risk of acute repetitive seizures and be aware of available options for their treatment in the outpatient setting. Additional research is needed to identify which specific treatments are best for different types of patients.

Introduction

Epilepsy is one of the most common neurologic conditions and affects over 70 million individuals worldwide [1]. While many patients' seizures can be controlled with antiseizure medications (ASMs), about one-third of patients with epilepsy will be refractory to ASMs [2, 3]. Among these patients, approximately 50% may experience acute repetitive seizures (ARS), also known as "seizure clusters," "repetitive seizures," "seizure flurries," and

"cyclic seizures" [4]. ARS is not defined in the International League Against Epilepsy (ILAE) Commission on Classification and Terminology but generally is used to describe multiple seizures in patients with epilepsy that occur within 24 h [4–8]. Seizure clustering is associated with worse long-term outcomes including increased mortality and decreased remission rates [9, 10], and increased risk of post-ictal psychosis [11, 12]. Appropriate treatment and prevention of ARS are therefore critical in the management of drug-resistant epilepsy.

Despite the prevalence of ARS among patients with epilepsy, the use of rescue medication (the mainstay in treatment and prevention of ARS) is surprisingly low. Fewer than 10% of patients report having a current prescription for a rescue medication [4]. Benzodiazepines remain the first-line treatment for acute seizures, but their use remains limited in the outpatient setting for multiple reasons. Prescribers may find it challenging to choose between different routes of administration. For newer drugs, the prior authorization process adds to clinician and administrative burden and inefficiencies of care. There is also likely a knowledge gap among clinicians regarding the dangers of ARS and the safe prescribing of these medications. Concerns about the potential for patients to develop benzodiazepine use disorder may further limit patient access to these therapies. It is very important for clinicians and patients with epilepsy to be aware that benzodiazepines remain first-line treatment; however, many patients either do not treat their ARS or only use their conventional ASMs and therefore miss the opportunity to stop the seizures rapidly.

Rectal diazepam was approved by the US Food and Drug Administration (FDA) in 1997 and remained the only available approved seizure rescue option for decades. Other non-evidence-based options have been used in clinical practice (e.g., sublingual lorazepam, clonazepam), but required prescribers to seek these out and often needed compounding pharmacies to prepare custom formulations (e.g., diazepam intensol oral solution) of these medications. Over the last decade, there have been multiple new rescue medications approved in the USA and worldwide. This article will review the current evidence-based treatments for ARS and best practices for their management.

Patient selection

The choice of a seizure rescue medication first depends on identifying patients for whom treatment is appropriate for the prevention of ARS. These patients are at increased risk of ARS evolving into status epilepticus [13, 14]. There are multiple factors associated with increased risk of ARS including catastrophic epilepsy syndromes such as infantile spasms, Lennox-Gastaut syndrome, Otahara syndrome [9], those with drug-resistant epilepsy (DRE) and high frequency of seizures [7], post-traumatic epilepsy [15], and patients who have a longer duration of epilepsy [16]. Patients with focal epilepsy and prior history of seizure clustering are also at increased risk [15], as well as those with symptomatic generalized epilepsy, history of central nervous system infection, epilepsy due to a cortical dysplasia, history of status epilepticus, early age of seizure onset, and intractable epilepsy [16]. Patients with epilepsy who are discharged from the epilepsy monitoring unit (EMU) after rapid ASM withdrawal are also at increased risk of seizure clusters [17, 18].

Routes of administration

There are multiple possible routes of administration for benzodiazepines in the treatment of ARS, with important considerations regarding availability, ease of use, rapidity of absorption and onset, safety, and cost. Intravenous (IV) administration is most commonly used by pre-hospital emergency medical services, emergency departments, and inpatient settings by healthcare professionals. While providing rapid onset of action with direct parenteral administration, the need for safe placement and use of an IV line may introduce delay in treatment and it effectively eliminates this option for use in the outpatient setting. Oral, rectal, intramuscular, buccal, nasal, and inhalation routes of administration are better suited for outpatient use. Clinical studies have shown that with the exception of oral ASMs, the average time to administration and time to seizure termination between different routes of administration are comparable and there is no clear evidence in favor of one route of administration over another (see Table 1). Oral administration of a seizure rescue medication requires patients to be able to safely swallow medication, which is often not possible during or after seizures, and may cause delay in effect given unpredictable absorption within the gastrointestinal (GI) tract, and first-pass metabolism effects by the liver. Rectal administration also requires absorption by the GI tract, but has the advantage of bypassing the portal circulation and first-pass elimination by the liver as the middle and inferior rectal veins drain directly into systemic circulation. The disadvantage of rectal administration is related to difficulty with its administration during a seizure, the discomfort of administering/receiving treatment in public, and inadequate dosing that may occur if medication is not retained in the rectal vault prior to absorption [19]. Intramuscular (IM) administration via auto-injector devices enables rapid treatment by medical as well as non-medical personnel. A major drawback of IM administration is pain at the injection site which could limit its adoption by individuals who may need frequent rescue

Table 1. Time to administration and time seizure termination for different routes of benzodiazepine administration reported from clinical trials of patients treated for seizure emergencies

Route	Average time to administration (min)	Average time to seizure termination (min)
Intravenous	4.8–20	0.3–5.7
Intramuscular	1.1–5.3	1.1–7.9
Rectal	1.1–12	0.6–15
Intranasal	0.8–5	2.3–7.5
Buccal	2–6.1	2.8–8
Oral		24.4

Adapted from [20]

therapy. Buccal administration with lipid soluble forms of medication that rapidly absorb into the oral mucosa typically involves the use of gel solutions or soluble films that readily dissolve. While relatively easy to administer, there is the potential risk of aspiration, and the oral mucosa may be inaccessible during an acute seizure.

The intranasal (IN) route has significant advantages over the other options. Administration is generally easy, does not require patient participation, is more socially acceptable, and provides rapid absorption/onset of action. Disadvantages to IN administration include treatment failure related to incomplete administration related to patient movement, poor technique, and possible nasal irritation. Orally inhaled administration of alprazolam, using a handheld inhaler device, is currently under investigation and is another option that holds promise for the reliable and rapid delivery and action of benzodiazepines. The mechanism of absorption is through delivery of an aerosolized, rapidly absorbed benzodiazepine deep into the lung tissue producing a fast, systemic effect. The main limitation to this technique is that it requires the patient be alert enough to actively inhale which may be difficult to coordinate, or not possible in patients who have altered awareness or experience significant apneic episodes during seizures.

Available treatment options

Appropriate and early treatment of ARS may reduce the need for hospital care and lessen patient anxiety and caregiver burden [21]. The goals of treatment are prevention of status epilepticus, hospitalization, and injury/death, and to avoid worsening of the underlying epilepsy. Below, we review the available FDA-approved (Table 2) and off-label options for treatment of ARS and the available evidence for their use.

FDA-approved options

Rectal diazepam

Rectal diazepam gel was approved for use in ARS in 1997. A single-blind randomized, crossover study comparing rectal diazepam gel to intravenous diazepam demonstrated that rectal gel formulation was rapidly absorbed and well-tolerated [22]. This study found that plasma levels of diazepam over 200 ng/mL could be achieved within 15 min, and a time to peak concentration in plasma of 1.18 h (compared to maximal plasma concentration of over 500 ng/mL attained in less than 1 min for intravenous formulation). This represented the first FDA-approved treatment for acute seizures that could be administered by caregivers in the home environment. The major drawback to this formulation is the route of administration. In a phase 3 safety study that surveyed patients and their caregivers on their experience using rectal vs. intranasal diazepam, 59.1% of caregivers reported that rectal diazepam

Table 2. FDA-approved rescue therapies for treatment of acute repetitive seizures

Generic	Brand	Year approved	Route	Dose	Second dose	Limits
Diazepam	Diastat	1997	Rectal	0.2 mg/kg (rounded up to nearest 2.5 mg; max 20 mg) or 10–20 mg as single dose	n/a	1 episode every 5 days, 5 episodes per month
Diazepam	Valtoco	2020	Nasal	0.2 mg/kg as a single dose	May be repeated once after 4 h	No more than 1 episode every 5 days, no more than 5 episodes per month
Midazolam	Nayzilam	2019	Nasal	One spray (5 mg) into one nostril	One additional spray (5 mg) into opposite nostril after 10 min	1 episode every 3 days, 5 episodes in 1 month

was not easy to administer, and 86.4% of patients were not comfortable with needing to receive rectal diazepam in public [19].

Nasal diazepam

Intranasal delivery of diazepam received FDA approval in 2020. A phase 1 bioavailability study demonstrated that the time to reach maximal plasma concentration of intranasal diazepam was similar to rectal gel [23]. A large open-label safety study showed similar safety profiles between diazepam nasal spray and rectal diazepam [24].

Nasal midazolam

Among alternatives to rectal diazepam, intranasal midazolam was approved by the FDA in 2019 for the treatment of acute seizures [25]. Prior to use for seizures, intranasal and buccal midazolam were used for initial anesthesia in young children, owing to their lipid solubility at physiologic pH, and their ability to readily cross the blood–brain barrier. A preliminary field trial to test the feasibility of use demonstrated a robust clinical response (79/84 patients responding) [26]. A clinical trial comparing intranasal midazolam to rectal diazepam in children showed superior responses with midazolam measured by successful cessation of seizure activity and decreased need for a second medication [27]. The ARTEMIS-1 trial (Acute Rescue Therapy in Epilepsy with Midazolam Intranasal Spray) compared IN midazolam 5 mg vs. placebo for the treatment of seizure clusters. Midazolam demonstrated improved treatment success defined as cessation of seizure activity within 10 min of administration, without recurrence of seizure [28]. In an open-label extension trial evaluating the safety of multiple doses of IN midazolam, treatment with a second 5 mg dose was safe and well-tolerated, with the most frequent side effects including nasal discomfort, somnolence, and headache [29]. After the first dose, 55.5% of seizure clusters resolved. Of the 40% of patients who received a second dose, 80% were successfully treated.

Non-FDA-approved options

Buccal midazolam

Owing to its ability to readily absorb across mucous membranes, midazolam has also been used for the treatment of acute seizures. In a randomized trial of pediatric patients at a residential school, buccal midazolam was found to be non-inferior to rectal diazepam [30]. A multicenter randomized trial in the UK showed midazolam was more effective in stopping seizures [31]. Doses were age-adjusted in this pediatric population, ranging from 2.5 to 10 mg. The non-inferiority of buccal midazolam to rectal diazepam in the emergency and residential settings has been demonstrated in multiple other

trials [32–35]. A trial in Iran comparing buccal midazolam to intravenous diazepam in the emergency department setting showed comparable rates of cessation of seizure activity [35].

Oral clonazepam

Clonazepam is available in oral disintegrating tablets in dosages including 0.125, 0.25, 0.5, 1.0, and 2.0 mg. There is limited data available to assess the use of oral clonazepam in the treatment of ARS. Compared to other benzodiazepines, it has a relatively prolonged onset of action (20–40 min) but a longer half-life than midazolam and lorazepam; thus, it may be more useful for the prevention of ARS after a single seizure rather than the abrupt cessation of seizure activity. To date, no prospective study comparing clonazepam to other treatments has been published. A study surveying patients and families using clonazepam disintegrating wafers reported mixed results regarding perceived efficacy compared to rectal diazepam [36].

Vagal nerve stimulation (VNS)

A proportion of patients with DRE have a VNS implanted for neuromodulatory therapy for their seizures. These devices provide chronic stimulation to the brain, but also have the option of a patient or caregiver using an external magnet to deliver a bolus of stimulation as needed. A number of patients find that the delivery of this extra bolus of stimulation can abort a seizure quickly, or reduce its duration or intensity [37]. It may also help to reduce or prevent clustering. This can be a valuable treatment option for some patients, and education regarding this should be reviewed with appropriate patients and caregivers. Some patients can combine using extra VNS bolus doses with benzodiazepines for acute seizures or ARS.

Seizure action plan and monitoring

Seizure action plans are personalized response protocols for the management of breakthrough seizures for individual patients. They provide guidance to patients and caregivers, and are a requirement of many schools and residential programs. The use of seizure action plans may help patients and their families self-manage their epilepsy, and more efficiently utilize available healthcare system resources. Despite these potential benefits, a Harris poll found that among patients who had experienced a seizure cluster in the previous year, only 30% had active seizure action plans [6]. A prospective clinical trial in pediatric patients with epilepsy found that the utilization of seizure action plans was associated with increased comfort among caregivers with regard to seizure care, as well as improved no-show rates in epilepsy clinic, compared to patients and caregivers who received standard epilepsy

care alone [38]. Studies examining the impact of seizure action plans on use of rescue medications and hospitalizations are ongoing (NCT02995759). Education regarding administration of rescue medications should be part of the development of seizure action plans. One study surveyed families of patients with epilepsy and found that despite a high frequency of prescribing rescue medication (87%), nearly 40% of families reported that they had not received any training in the administration of rescue medication [39]. These data underline the important role of the treating clinician in not only prescribing first-line treatment for ARS, but also in the effective education for patients and caregivers. Teaching should include the use of training devices (e.g., nasal injectors), and use of freely available resources for families, providers, and schools.

Future options

Inhaled alprazolam

The development of benzodiazepines delivered by oral inhalation represents an exciting development in the treatment of acute seizures. Due to the large surface area of the lungs, the administration of inhaled benzodiazepine aerosols has the advantage of very rapid delivery of medication into the systemic circulation. A phase 2a, multicenter, randomized, double-blind, crossover, placebo-controlled study in patients with photosensitive epilepsy demonstrated that inhaled alprazolam rapidly suppressed the electroencephalographic photoparoxysmal response [40]. A subsequent clinical trial is ongoing to assess the use of single-dose inhaled alprazolam in the termination of acute seizure and prevention of ARS (NCT05077904).

Conclusions

Benzodiazepines remain the first-line rescue therapy for acute seizures and ARS. There are multiple effective options and formulations available. Additionally, there are ongoing studies investigating new routes of administration, particularly the use of inhaled benzodiazepines, that present new options that can help decrease caregiver burden. Trials focusing on which specific treatments are best for different types of patients may further help refine use of these agents. For example, though intranasal diazepam and midazolam are both currently available FDA-approved treatments, it is yet not known if one is superior or should be prescribed for particular patients or seizure types. In the end, some of these decisions may be dictated by cost and local availability of particular medication formulations. Other issues related to the use of benzodiazepines for ARS include educating prescribers and patients on when to use, and when not to use them, including recognizing and defining

clusters. This will help to avoid overuse, which may lead to habituation and decreased efficacy, or development of a use disorder. Further studies are needed to directly address these issues.

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