Acute Management of Seizure Clusters and Prolonged Seizures: A Review of Rescue Therapies

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Patients with epilepsy who experience seizure clusters or prolonged seizure episodes can benefit greatly from the use of rescue therapies. Rescue therapies are often used to prevent prolonged seizures from progressing into status epilepticus and to prevent seizures from clustering. Benzodiazepine rescue medications are the first-line treatment for seizure clusters or prolonged seizures. In addition to rectal diazepam, a widely used formulation approved by the US Food and Drug Administration (FDA), the FDA recently approved intranasal midazolam and intranasal diazepam for use as rescue medications to treat seizures in paediatric and adult populations. In addition to medications, implantable devices such as responsive neurostimulation can help predict and prevent seizures. This article is a literature review assessing currently available formulations of rescue medications and highlighting new formulations, devices, and novel drug delivery systems currently in research and development.

Keywords

Benzodiazepines, drug delivery systems, epilepsy, prolonged seizure, rescue medication, seizure cluster

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Rescue medications are an important part of the treatment regimen for patients with intractable epilepsy, specifically those who experience seizure clusters or prolonged seizure episodes. Rescue medications are prescribed to end seizure activity quickly and effectively in order to prevent further seizure-related morbidities and prevent seizure recurrence. An ideal rescue medication is stable at room temperature, easy to administer, works rapidly to cease seizure activity and has consistent, reliable absorption that allows it to take action rapidly. Intravenous benzodiazepines are used by trained and qualified healthcare providers to treat seizure clusters or status epilepticus but are not safe or feasible for home use. Currently, three rescue medications have been approved for use in the USA by the US Food and Drug Administration (FDA): diazepam rectal gel (Diastat®; Valeant Pharmaceuticals, Laval, Canada), midazolam intranasal spray (Nayzilam®; UCB, Brussels, Belgium), and diazepam nasal spray (Valtoco®; Neurelis, Inc., San Diego, CA, USA).[1–3] In Europe, South America and some Asian countries, buccal midazolam (Buccolam®; Neuraxpharm, Barcelona, Spain) is used to manage prolonged seizures in paediatric and adolescent populations.[4] Buccal midazolam can also be used off label in adult populations. Furthermore, on-going studies are assessing the safety and efficacy of intramuscular and intrapulmonary administration of benzodiazepines to terminate seizures (Pediatric dose optimization for seizures in emergency medical services (PediDOSE); ClinicalTrials.gov identifier: NCT05121324).[5,6] In this review article, we assess currently available formulations of rescue medications in the acute management of seizure clusters and prolonged seizures, while also highlighting new formulations, devices, and novel drug delivery systems that are currently in research and development stages.

Defining seizure cluster and prolonged seizure

Seizure clusters

For the purpose of this review, seizure clusters are defined as "acute episodes of increased repetitive seizures, irrespective of type or grouping, that differ from the person's usual seizure pattern".[7] For rescue medication to be administered correctly, the onset of the seizure must be readily recognized by the patient or caregiver.[4]

Seizure clusters have been variably defined in the literature as two or more seizures in a 6-hour period, three or more seizures over 24 hours, or two to four seizures in less than 48 hours.[8] They have been investigated mainly via prospective studies involving seizure diaries.[9,10] Statistical methods have also been used to identify seizure clusters. These algorithms test the hypothesis that seizures are randomly distributed in time and identify deviations from this pattern. Predictive factors for seizure clusters included high seizure frequency and prior seizure clusters, as observed by a prospective study of 247 patients with epilepsy aged ≥14 years.[9] This study found a prevalence of seizure clusters of 29.1% in this patient population, which included a large proportion of patients who had no seizures over the year of follow-up (n=110). The prevalence of seizure clusters over the following year increased to 62.7% in patients with a history of seizure clusters.[9] Another prospective study using seizure diaries reported a 29% prevalence of seizure

clusters and found an association with extratemporal epilepsy, remote symptomatic seizures and a history of convulsive status epilepticus.[10]

In patients with refractory focal epilepsy, seizure cluster prevalence of 57% has been reported, underscoring that patients with medically refractory epilepsy are at the highest risk.[8] Additionally, in a sample of patients with status epilepticus, one study found 44% of patients suffered from seizure clusters compared to 12.5% without clusters.[4]

Prolonged seizures

The definition of a prolonged seizure is dynamic, as it is based on the typical individual seizure duration seen in a patient. A seizure that lasts two to three times the normal duration of an individual's seizures could be considered a prolonged seizure. Rescue medications can also be used to treat prolonged seizures. Although they are used as off-label medications for the treatment of these seizures, this strategy is often employed by healthcare providers, with instructions for patients and caregivers to use rescue medication if seizures persist for >5 minutes.

Prolonged seizures have a higher likelihood of developing into status epilepticus and, therefore, represent a key time-point for early intervention by caregivers.[11] The International League Against Epilepsy defines status epilepticus as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures".[12] The time point at which the normal mechanisms for spontaneously stopping seizures have failed is 5 minutes for convulsive seizures, 10 minutes for focal seizures with and without impairment of consciousness, and 10 minutes for generalized absence seizures.[12] The treatment of prolonged seizures with rescue medications can prevent progression to status epilepticus, which, in addition to high morbidity and mortality, results in irreversible neuronal injury and the alteration of seizure networks.

Rescue medications can also be employed for prolonged seizures to stop progression to more disabling seizure types. For example, rescue medication during a prolonged aura can stop the progression to bilateral tonic-clonic seizures or prevent the progression of a focal aware seizure to a focal impaired aware seizure.[13]

Seizure action plans

The Seizure Cluster Burden of Illness US survey conducted by the Epilepsy Foundation in 2014 assessed 861 clinicians, patients, and caregivers and found that, although 52% of clinicians reported that over half of their patients had a seizure action plan in place, only 30% of the surveyed patients reported having seizure action plans.[14,15] Since 2014, both midazolam intranasal spray and diazepam intranasal spray have gained FDA approval.[2,3] The convenience and efficacy of intranasal medications compared with rectal diazepam gel (the only FDA-approved rescue medication in 2014) could contribute to an increase in patient and caregiver compliance with seizure action plans.

Drug delivery systems

There are many formulations of rescue medications that differ in route, dose and active ingredient, providing a variety of options for prescribers and patients. The drug delivery systems discussed in the contemporary literature include intranasal, rectal, intrapulmonary, intramuscular, intravenous, buccal and sublingual administration (*Table 1*).[4,8,13,14,16–26] In this article, we do not explore all of the aforementioned drug delivery systems but instead briefly describe the most commonly used and clinically relevant methods of rescue medication administration. The pharmacokinetics and pharmacodynamics of the same medication can vary based on the route of entry. Ensuring that a rescue medication is easy to use, efficacious and with minimal side effects can help increase patient compliance, especially when supplemented with physician-directed education and instructions for use.

Intranasal

The intranasal route offers reliable access to the circulatory system due to the nasal cavity's high vascularity.[27] The cells of the nasal cavity contain highly vascularized microvilli, which significantly increases the surface area in the nose and allows for rapid uptake of medication (bypassing first-pass metabolism). The nerve cells within the nasal cavity provide a direct route to the nervous system for rescue medications to take their effect. Some disadvantages of intranasal medications are the limited amount of medication that can be delivered into the nasal cavity and the consideration that intranasal administration can be blocked by nasal obstruction and facial trauma.[28,29] This is especially true in the case of full-body acute repetitive seizures, where there is a risk of falls and trauma secondary to seizure.[30]

Rectal

The rectal route is also highly reliable and can be used when the nasal route is inaccessible or otherwise compromised.[31,32] Medications delivered rectally have a faster speed of onset, bypass first-pass metabolism and subsequently have a higher bioavailability than those delivered orally, as the lower rectum absorbs medication directly into the bloodstream.[31,32] However, the rectal route is not without disadvantages. The contents of the rectum at the time of administration can affect the efficacy of the rescue medication, and interpatient heterogeneity of response to rectal medications has been observed.[33] Furthermore, patients and caregivers are often concerned about the stigma and embarrassment of giving rectal medication in public environments.[16] Rectal medications can also be difficult to administer rapidly to larger patients and patients with disabilities (e.g. wheelchair-bound patients).[17]

Intrapulmonary

The intrapulmonary route is advantageous because of the large surface area and highly vascularized lung tissue, which allows the rapid and consistent absorption of medication with both systemic and local effects.[34] Intrapulmonary administration also bypasses first-pass metabolism and allows for increased bioavailability compared with oral medications.[35] With proper training and patient education, the intrapulmonary route may be a promising way to administer rescue medications due to its rapid effects and the ability for patients or caregivers to easily self-administer.

Intramuscular

Though intramuscular autoinjectors have not been approved by the FDA for the administration of seizure rescue medication, they have been approved to deliver rescue medication for other conditions. Intramuscular delivery systems show rapid effects (within 2 minutes of administration) and bypass first-pass metabolism, but non-autoinjector delivery of intramuscular medication can be difficult in the outpatient setting, especially for nonmedical personnel.[36,37] The high vascularity of skeletal muscles ensures that the medication rapidly reaches the circulatory system and exerts its effect. The rate of absorption is most rapid for intramuscular injections administered in the upper arm, followed by injection into the lateral thigh and, lastly, the buttocks.[38] Complications with intramuscular injection are typically related to administration. Variations in the thickness of subcutaneous fat can cause the medication to be delivered subcutaneously (significantly slowing down the time to onset).

Table 1: A brief overview of rescue medications[4,8,13,14,16–26]

Route	Medication	Half-life (hours)	Time to onset (minutes)	Advantages	Disadvantages	Who can administer
Intravenous	Lorazepam	12–14[18,23]	1–3[17]	Rapid and reliable onset of action; bypasses metabolism directly into the bloodstream. Extremely reliable	Complex administration, limited to medical environments with advanced medical providers;[23] IV site must be placed, which takes time and increases the risk of infection[17]	Trained medical professionals[17]
Intra-pulmonary	Alprazolam	6–15 (oral, IV)*[17]	30 seconds–2 minutes[4,13]	Large surface area of lungs allows for rapid and efficient absorption;[19] targeted to termination of ongoing seizures[13]	It may be difficult to administer during impaired aware seizures, however, active inhalation is not necessary for efficacy;[13] cough, somnolence, dysgeusia[13]	Patient, caregivers[13]
Intranasal	Diazepam	49[14,23]	2–10[23]	Easy to administer;[16] bypass first-pass metabolism;[23] minimal risk of injury[19]	Limited amounts of medication can be delivered;[20] facial trauma or nasal obstruction can prevent administration;[20] nasal discomfort, somnolence[8,20]	Patient, caregivers[13]
Intranasal	Midazolam	2–6[14,22]	3–10[4,17]	Easy to administer;[16] low risk of incorrect dosing; minimal risk of injury	Limited amounts of medication can be delivered;[20] facial trauma or nasal obstruction can prevent administration;[20] nasal discomfort, somnolence[8,20]	Patient, caregivers[16,17]
Intramuscular	Midazolam	2–5[17,23]	5–15[21,23]	Bypasses first-pass metabolism;[23] stable formulation without refrigeration;[25] prolonged effects[25]	Limited amounts of medication can be delivered; variable absoprtion;[23] haematoma, pain[4]	Patient, caregivers (trained with autoinjector)[17,23,26]
Buccal	Midazolam	2–4[17,23]	5–15[23]	Rapid effect;[22] bypasses first-pass metabolism[23]	Medication placement and retention can be difficult in active seizures;[17] restricted to children and adolescents;[19] inconsistent absorption due to ictal hypersalivation and buccal secretion;[20] potential aspiration risk[4]	Patient, caregivers
Rectal	Diazepam	45–46[14]	2–5[17]	Low infection risk;[23] bypasses first-pass metabolism[17,23]	Difficult to administer in adults or older children;[17] the procedure can be invasive and uncomfortable, especially in public areas;[16] lethargy, defecation, diarrhoea[4]	Caregivers
Sublingual	Lorazepam	12–15[24]	15–17[23]	Bypasses first-pass metabolism;[23] rapid absorption[23]	Variable absorption;[23] medication placement/retention can be difficult in active seizure;[17] aspiration risk[4]	Patient, caregivers

** Note: Studies to characterize the pharmacokinetic profile of intrapulmonary alprazolam are ongoing*
IV = intravenous.

Properties of benzodiazepines

Benzodiazepines are the most commonly prescribed rescue medication for seizures as they have proven efficacy and are the first-line treatment for status epilepticus.[39] Due to their hydrophobicity and inherent lipophilicity, benzodiazepines easily diffuse across the blood–brain barrier to take action in aborting seizure activity. Benzodiazepines contain a heterocyclic ring system with a benzene ring fused to a diazepine ring system. They act as central nervous system depressants through an allosteric interaction with the γ-aminobutyric acid (GABA) receptors of the A-type ($GABA_A$) that increases the affinity of the receptor for GABA.[26,40,41] This modulation induces a hyperpolarized cellular state due to an influx of chloride ions, leading to a reduction in seizures and nervous system depression as a result of synaptic inhibition.[26,40,41]

Currently available rescue medication approved by the US Food and Drug Administration

Rectal diazepam gel

In 1997, rectal diazepam gel received the FDA approval for the treatment of cluster seizures in patients 2 years or older.[1,42] Because of its rapid absorption and limited side effects, rectal diazepam gel continues to be used widely as a rescue medication to treat acute seizures outside the hospital environment. The time to peak plasma concentration after administration (T_{max}) for rectal diazepam is around 70 min.[43] A 15 mg dose of rectal diazepam gel has a half-life of ~46 hours, which reduces the risk of withdrawal. Despite the efficacy of rectal diazepam gel, patients and their families often express discomfort with its administration, especially in public settings, because of the difficulty and vulnerability of the procedure.[16]

Diazepam nasal spray

Diazepam nasal spray was approved by the FDA for the acute treatment of seizure clusters or other stereotypic epileptic episodes for patients 6 years of age or older.[3,44] The T_{max} for diazepam nasal spray solution is 90 minutes, and diazepam nasal spray demonstrates an absolute bioavailability of 97%.[45] Of note, T_{max} does not indicate time to seizure cessation or time to efficacy, as many medications exhibit effects well before they reach the peak plasma concentration.[14] Diazepam nasal spray is lipophilic and rapidly redistributes into adipose tissue, resulting in an abbreviated duration of antiseizure properties despite its known half-life of 49 hours.[46] Intranasal diazepam has comparable bioavailability to rectal diazepam gel, but the nasal formulation demonstrates a more consistent interpatient pharmacokinetic profile and uses a more convenient, comfortable route of administration.[47] The intranasal formulation of diazepam is advantageous as a rescue medication betablecause of its easy administration and the potential for self-administration, which reduces the rate of dosing errors and the difficulty of the procedure for nonmedical patient caregivers.[16,48,49]

An open-label study with 46 healthy participants was performed to compare diazepam nasal spray to rectal diazepam gel.[33] This study found that there were fewer reports of somnolence in the intranasal diazepam group (56.5%) than in the rectal diazepam gel group (89.1%). In order for a rescue medication to consistently take effect, it is important to analyse the potential for patients to develop a tolerance and subsequently experience a decrease in the efficacy of a prescribed rescue medication. In 2019, a phase III, open-label, repeat-dose safety study (ClinicalTrials.gov identifier: NCT02721069) showed that no tolerance to diazepam nasal spray was observed when it is used with intermittent repeat dosing to treat seizure clusters in patients with epilepsy.[44,50,51] To gauge the effectiveness of diazepam nasal spray, this study examined how many patients on concomitant benzodiazepine therapy required a second dose of Valtoco on the same calendar day to address seizures.[50] Dosing was recorded in a patient diary, and only 9.3% of the logged diazepam nasal spray doses were second doses.[50] These findings, in conjunction with the retention rate of 82.9% after a median 13-month treatment period, suggest both the efficacy and tolerability of intranasal diazepam as a rescue medication for seizure clusters.[50]

However, the potential for nasal obstruction due to seasonal allergies or other causes of rhinitis is of concern. The results of the phase III study from 2019 reported that patients with a history of seasonal allergies did not experience a significant discrepancy in the observed effects of intranasal diazepam compared with patients without seasonal allergies.[51] Of the 62 patients with allergies, 11.1% reported using a second dose of diazepam nasal spray within 1 day of the first dose compared with 7.8% of the 96 patients without allergies.[51]

Midazolam nasal spray

Midazolam intranasal spray is another FDA-approved option for treating seizure clusters in patients 12 years of age or older. A clinical trial comparing midazolam intranasal spray to rectal diazepam gel in children showed superior responses with midazolam intranasal spray as measured by the successful cessation of seizure activity and the decreased need for additional medication.[52] The T_{max} for midazolam intranasal spray is between 9 and 19 minutes compared with between 70 and 90 minutes needed for rectal diazepam gel and intranasal diazepam, respectively.[8,14,43] However, intranasal diazepam showed a more favourable bioavailability profile of 97% than the 62–73% bioavailability of midazolam intranasal spray.[38] Seizure interruption was observed within 3–10 minutes post-administration of midazolam intranasal spray, which is comparable to the 2–10 minute seizure interruption of rectal diazepam gel post-administration. In clinical trials, midazolam intranasal spray outperformed rectal diazepam gel in the interruption of seizure activity, with 86.3% of patients seeing seizure clusters resolved within two doses of midazolam intranasal spray compared with a termination rate of 60% in the rectal diazepam gel group.[52,53] In a randomized, double-blind, placebo-controlled trial, a significantly greater proportion of patients receiving midazolam intranasal spray experienced treatment success (defined as the cessation of seizure within 10 minutes and no recurrence 10 minutes to 6 hours after trial administration) compared with the placebo arm (53.7% versus 34.4%; p=0.0109).[20]

Current recommendations

A September 2019 survey of clinicians revealed that midazolam intranasal spray would be the preferred rescue medication for developmentally normal older paediatric patients (16 years old), while rectal diazepam gel continued to be favoured for younger patients and patients with developmental challenges.[32]

Medications in clinical trials, those that are not yet approved by the US Food and Drug Administration and medications approved for use in Europe or Asia

Inhaled alprazolam

There is great interest in exploring the intrapulmonary route for rescue medication delivery for cluster and prolonged seizures because of its ease of administration and rapid onset.[54] There are currently clinical trials underway using inhaled alprazolam, which is administered by the Staccato® (Alexza Pharmaceuticals, Fremont, CA, USA) device. Alprazolam was selected over other common benzodiazepines due to its higher vapour point and thermal stability.[38] The ENGAGE-E-001 study, a double-blind, proof-of-concept, inpatient phase IIb clinical trial (ClinicalTrials.gov identifier: NCT03478982) that was completed in 2020, demonstrated the efficacy of Staccato® alprazolam in terminating or preventing stereotypical seizure episodes in patients with either focal or generalized epilepsy.[13] This study found that 65.8% of participants who received 1 mg (n=30) or 2 mg (n=38) doses of alprazolam via the Staccato® device responded to treatment compared with 42.5% of patients who received placebo (n=40).[13] The median time-to-seizure cessation for patients receiving Staccato® alprazolam was 30 seconds compared with 60 seconds to seizure cessation observed in the placebo group.[13] The use of chronic benzodiazepines had minimal effect on the efficacy of alprazolam. The Staccato® alprazolam device is currently being investigated in a phase III, double-blind study for use in an outpatient setting to treat stereotypical seizure episodes with prolonged or repetitive seizures in patients aged 12 years and older (ClinicalTrials.gov identifier: NCT05077904).[6] The rapid onset of action of alprazolam and its ability to terminate on-going seizures sets it apart from other agents.

Buccal midazolam

Buccal midazolam has been approved in the EU, South America, and some Asian countries as a rescue medication for the treatment of prolonged convulsive seizures in patients between the ages of 3 months and 18 years.[4] No other approved rescue medications in available for the treatment of prolonged convulsive seizures for paediatric patients as young as 3 months by non-healthcare professionals in an outpatient setting. McIntyre et al. observed that buccal midazolam outperformed rectal diazepam gel in the interruption of seizure activity and was associated with reduced respiratory depression.[55] A 2008 Ugandan single-blind study with 330 patients also

showed that buccal midazolam was superior to rectal diazepam for the acute treatment of prolonged seizures in patients aged 3 months to 12 years, with a 26.5% failure rate with midazolam versus 55.9% failure rate for rectal diazepam gel (p=0.002) and a comparable median times-to-seizure cessation (4.75 versus 4.35 minutes, p=0.518).[56] They also observed that, in a subgroup of patients who experienced seizure recurrence after initial seizure control, patients who were administered buccal midazolam displayed a longer median time to recurrence (1.8 hours for rectal diazepam versus 5.11 hours for buccal midazolam; p=0.001).[56] The authors noted the easier administration, lower cost, increased stability at room temperature and lower risk for respiratory depression associated with the use of buccal midazolam compared with rectal diazepam. These findings further support the use of buccal midazolam as a rescue medication for the treatment of acute repetitive seizures outside the hospital.

Intramuscular midazolam

In 2012, the RAMPART study (Rapid Anticonvulsant Medication Prior to Arrival Trial; ClinicalTrials.gov identifier: NCT00809146) compared the efficacy of intramuscular midazolam with intravenous lorazepam and found that intramuscular midazolam is at least as safe and effective as intravenous lorazepam.[57] A total of 329 of 448 (73.4%) patients in the intramuscular midazolam group and 282 of 445 (63.4%) patients in the intravenous lorazepam group arrived at the emergency department seizure free.[57] It takes an average of 8 minutes from the initiation of drug administration to seizure cessation for all intravenous benzodiazepines, and 5 minutes on average for intramuscular midazolam.[26] Although intravenous benzodiazepines have a rapid onset upon administration, the time needed to establish venous access eliminates the time advantage associated with intravenous treatment. The benefits of a midazolam autoinjector over intravenous rescue medication administration include ease of use, rapidity of administration and portability. Midazolam, unlike lorazepam, is stable at room temperature and does not need refrigeration.[57] These findings support the use and development of approved intramuscular autoinjectors to treat prolonged seizures in a prehospital setting. Intramuscular midazolam is not currently approved by the FDA as a seizure rescue medication; however, pending FDA approval, Pfizer plans to produce an intramuscular midazolam autoinjector available for use by healthcare professionals.[38]

Considerations for prescribers

Safety and tolerance

While benzodiazepines are the standard of care for the treatment of seizure clusters and have a robust safety profile with short-term use (maximum 1 month), their long-term use is associated with a myriad of risks and adverse effects, including impaired motor function, respiratory depression, sedation, tolerance, benzodiazepine withdrawal syndrome, overdose and death.[58] The phenomena of cross-tolerance, as observed in mice, shows how the overuse of one benzodiazepine (e.g. diazepam) can render other benzodiazepines and even other antiepileptic medications such as valproate ineffective.[59] Provided that these findings are applicable to human subjects, cross-tolerance could complicate the treatment of seizures for the neurologist.

Benzodiazepine use in special populations

Benzodiazepine use for geriatric patients is allowed but cautioned by the American Geriatrics Society as data concerning the use of benzodiazepine rescue medications for older adults are limited.[60]

There is some evidence of adverse effects associated with benzodiazepine use during pregnancy, such as floppy infant syndrome and cleft palate.[61] However, due to the importance of seizure prevention, patients that are pregnant with a history of epilepsy, including patients with acute repetitive seizures, are encouraged to remain on their benzodiazepine prescriptions if there are no other alternatives. The American College of Obstetricians and Gynecologists recommends that patients currently prescribed antiepileptic medications consult with a multidisciplinary care team, including a neurologist and obstetrician-gynaecologist for gynecologic matters.[62]

Next steps and future delivery methods

Transdermal and implantable microchips

The development of controlled-release transdermal or implantable microchips could be worth investigating for the treatment or prevention of seizures in patients with epilepsy. Research is being conducted into creating solid-state silicon microchips able to release chemical substances on demand in a continuous or pulsatile manner.[35] Additionally, there are studies of controlled-release iontophoretic transdermal devices equipped with the ability to respond to stimuli such as electric or magnetic fields, ultrasound, light, or enzymes.[35] Although transdermal drug delivery systems are not currently indicated for use as rescue medications, the ability to detect and administer antiepileptic medication based on electrical stimuli is compelling due to the rapid increase in electrical activity displayed by the brain during seizures.

Responsive neurostimulation

Seizure detection algorithms, including intracranial electroencephalogram monitoring devices such as the responsive neurostimulation (RNS®) system, are uniquely capable of identifying and quantifying seizure frequency and patterns over time.[63] Many seizures are unnoticed by patients, particularly if they have no overt clinical manifestation or if seizures occur during sleep or impaired awareness. Further developments in real-time seizure detection technologies, such as the RNS® system will couple advances in seizure prediction and detection algorithms with the use of rapidly acting seizure rescue medications.

Patients can be warned that seizures will have a high likelihood of occurring over a set time frame. Seizure forecasting allows patients and their caregivers to employ rescue medications, temporarily increase doses of maintenance medication and minimize activities during higher-risk time periods. This can also decrease the side-effect burden of multiple maintenance seizure medications, instead using rescue medications and increasing maintenance doses when seizure clusters or prolonged seizures have the highest likelihood of occurring.[38,64]

Conclusions

The choice of method and medication for a patient should be specifically tailored to the clinical scenario. For example, patients with multiple short-interval seizures in a cluster may benefit from midazolam intranasal spray, whereas patients with seizures with a longer seizure cluster interval may be better candidates for diazepam nasal spray. The use of rescue medications for seizure clusters and prolonged seizures has improved patient care by decreasing emergency room visits and hospitalizations, preventing injuries from seizures, decreasing the chance of progression to status epilepticus and lowering the overall morbidity and mortality of epilepsy. Critical steps for the proper use of rescue medications include correctly identifying patients who will benefit from them, formulating comprehensive seizure action plans, and educating caregivers and patients on the use of rescue medications.[4] Rescue medications can empower patients and caregivers to intervene early and effectively at home or in the community to achieve improved seizure control. Although respiratory depression may occur with the use of benzodiazepines for rescue, the risk of seizures carries a greater risk

of respiratory compromise. Further development of rapid drug delivery systems and new molecules shows promise for enhanced management of recurrent seizures, seizure clusters and prolonged seizures. ❑

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