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Review

Seizure clusters, rescue treatments, seizure action plans: Unmet needs and emerging formulations

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ABSTRACT

Purpose of review: The aim of the study was to provide an overview of the prevalence, risk factors, burden, and current and emerging pharmacologic treatments for seizure clusters in patients with epilepsy.
Recent findings: Close to half of patients with active epilepsy experience seizure clusters, and the clinical, social, and financial burdens of seizure clusters are high. However, there is no widely accepted definition of seizure clusters; their prevalence is underappreciated, contingencies for addressing them (seizure action plans) are often lacking, and their effects are not well-studied. These issues have resulted in an insufficient number of investigations and approved medications for this condition. Novel formulations are in late-stage development to meet this unmet need.

1. Introduction

An estimated 30% of patients with epilepsy experience uncontrolled or poorly controlled seizures, despite treatment with antiepileptic drugs (AEDs) [1]. In some patients, on-treatment seizures appear to occur in clusters—2 or more within a relatively short time period, with return to baseline alertness in between. Terms such as *seizure clusters*, *serial seizures*, *seizure flurries*, and *acute repetitive seizures* (ARS) have been used, often interchangeably, to describe bouts of frequent seizures in patients with epilepsy [2–8]. However, despite the efforts of national and international health care agencies and epilepsy-focused advocacy groups, standardized terminology is yet to be defined and widely accepted.

In the mid-1990s, the National Institutes of Health (NIH) Epilepsy Advisory Committee and the US Food and Drug Administration (FDA) Peripheral and Central Nervous System Drugs Advisory Committee offered a standardized definition in response to the need to define the condition (they termed it "acute repetitive seizures") and to facilitate evaluation of potential treatments [3–5]. The defining features of ARS, according to these committees, included the occurrence of multiple seizures within a defined period, despite optimal/maximal therapy with antiseizure drug(s); severe complex partial or generalized seizures; a seizure pattern distinguishable from a patient's "normal" pattern with respect to type, duration, frequency, and/or severity; onset clearly distinguishable (by patient, caregiver, or healthcare professional) from the patient's "typical" seizures; and recovery between seizures [4–6]. These features, in various combinations, have been used to define populations in clinical studies of rescue therapies for patients experiencing seizure clusters [6].

The pathogenic mechanisms underlying seizure clusters remain unclear [8,9], and this knowledge gap represents a critical unmet need for this condition. It is not yet understood whether the mechanisms involved in drug-refractory epilepsy (e.g., overexpression of drug efflux pumps, altered structure/function of voltage-gated ion channels) are the same as those in seizure clusters [10]. Potential pathogenic factors include failure of seizure-terminating mechanisms and increased focal neuronal excitability [7,9,11]. It has also been hypothesized that seizure clusters may represent a "self-triggering" mechanism and that shorter seizures are less likely than longer seizures to sufficiently activate seizure-termination mechanisms [12].

This review provides an overview of seizure cluster prevalence, risk factors, burden, and associated risks for progression in patients with epilepsy and examines the current and emerging pharmacologic rescue treatment landscape.

2. Prevalence, risk factors, and disease burden of seizure clusters

2.1. Prevalence

Estimates regarding prevalence of seizure clusters among patients with epilepsy vary widely and depend on the definition applied and

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the study population [6,7]. *Clustering* has been defined on the basis of both seizure frequency (*x* seizures within *y* hours) and, as determined with statistical methods, timing patterns that differ from the patient's normal on-treatment seizure patterns; statistical methods typically generate lower prevalence estimates than frequency-based methods [4]. Using data from epilepsy specialty practices may lead to overestimates of clustering prevalence, because these data sets typically include patients with more severe or intractable epilepsy versus the overall population of patients with epilepsy [13]. A 2015 review reported that the prevalence of seizure clusters ranged from 13% to 76% for outpatient studies and from 18% to 61% for inpatient monitoring studies [3]. Estimates of seizure cluster prevalence reported in recent studies are summarized in Table 1. In a recent prospective study designed to determine the prevalence of clusters, defined as ≥2 seizures within a 6-hour period, 46% of patients with active epilepsy (≥1 seizure within prior year) had ≥1 cluster within the observation year [6]. This included a cluster prevalence of 30% in those who reported never having had a day with >1 seizure within the year prior to enrollment, and 63% in those who reported a day with ≥1 seizure within that prior year. Six-hour clusters occurred in 71% of patients who reported having >4 seizures within the prior year.

2.2. Risk factors

Several prospective studies have attempted to identify risk factors for seizure clusters, typically based on assessment of demographic and clinical factors, as well as seizure history, at baseline [3,6,8,13–16]. Reported risk factors include previous head trauma, extratemporal seizure localization, extratemporal spikes and/or slow-wave abnormalities on electroencephalogram, mean number of prior-month seizures, history of convulsive status epilepticus or of nonstatus epilepticus seizure hospitalizations [3,8,13], higher frequency of seizures at diagnosis [14] or during follow-up [6], intractable epilepsy (failure of ≥2 AEDs, lack of 1-year seizure-free periods), symptomatic generalized epilepsy, focal epilepsy (vs idiopathic generalized epilepsy), history of central nervous system infection, status epilepticus, early age at epilepsy onset [15], longer epilepsy duration, poor seizure control or more severe epilepsy, and history of seizure clusters [3,8].

The wide range of reported risk factors reflects, in part, the use of various seizure cluster definitions and study populations, as well as inclusion of patients with varying degrees of severity of epilepsy. For some of the smaller studies, relatively small variations in the reported incidence of seizure clusters may have influenced the statistical significance of results. However, more severe epilepsy (greater severity/frequency of seizures), poor seizure control, history of status epilepticus and/or epilepsy-related hospitalizations, and inadequate response to AEDs—all features of severe, refractory epilepsy—appear to be consistently associated with increased risk for seizure clusters.

2.3. Disease burden

In 1996, Mitchell was the first to note the importance of effective rescue treatment in attenuating the risk for progression from seizure clusters to status epilepticus [2]. In 2006, Haut emphasized the need to promptly treat seizure clusters to reduce the risk for disease progression and called out the potential for seizure clusters to confound the ability to properly localize epileptogenic foci in presurgical monitoring units [9].

In 2007, in a comprehensive discussion of the personal and financial burdens of repetitive and prolonged seizures, O'Dell and colleagues highlighted several areas of specific concern [17]. Health-related quality of life is negatively affected by seizure severity and frequency, degree of disability, family dynamics, and an overarching sense of worry and loss of control over one's situation. Seizure-related self-injury risk, which generally correlates with increased seizure frequency and severity, may also be elevated in patients with seizure clusters. Financial burdens include reduced income potential and increased risk for unemployment/underemployment, as well as higher direct and indirect costs of medical care [17].

In a long-term Finnish prospective observational study, patients newly diagnosed with epilepsy (N = 120) were followed up for a mean of 37 years (median, 40 years; range, 11–42 years). During that time, those with seizure clusters were significantly less likely than those without seizure clusters to achieve remission during treatment and were more likely to have drug-resistant epilepsy; they also had a higher mortality rate [14]. More recently, a US survey-based study of disease burden in 861 respondents (259 adult patients with seizure clusters, 263 caregivers, 339 clinicians) [18] found that the perceived impact of seizure clusters was greater among patients and caregivers than clinicians. Almost 70% of patients with seizure clusters reported an association with negative career effects, and most patients also reported that seizure clusters led to exhaustion, mental slowness/confusion, stress, and a sense of helplessness and fear. Most respondents reported that seizure clusters had made patients' lives miserable. Moreover, the majority of caregivers reported that patient care had a negative effect on their own health and quality of life [18]. It should be noted that a prospective study of patients with epilepsy (N = 247) found that those with seizure clusters were not at increased risk for injuries or emergency department (ED) visits. In this study, isolated seizures versus seizure clusters were found to be more strongly associated with seizure-related injuries (88% vs 12%, respectively) and ED visits (76% vs 24%), though the associations between seizure type and injuries or ED visits were not significant ($P = 0.137$ and $P = 0.272$, respectively) [6].

In summary, although estimates vary widely, seizure clusters are highly prevalent among patients undergoing medical treatment for epilepsy. Seizure clusters appear to be associated with more severe disease and are associated with substantial burdens across multiple domains, including clinical (potential for disease progression/premature mortality), health-related quality of life, and financial. These observations strongly suggest that an outpatient rescue strategy, including acute rescue treatments for seizure clusters, is essential and should be introduced as part of a management plan upon diagnosis of epilepsy [5,7].

3. Treatment of seizure clusters: unmet needs and current landscape

3.1. Undertreatment

Given the unpredictable nature of seizures and seizure clusters, adequate treatment of seizure clusters involves 3 phases: developing and becoming familiar with an action plan to be implemented in the event of a seizure; ensuring necessary medications are obtained and are carried with the patient and/or are accessible at all locations frequented by the patient; and implementing the action plan on first signs of a seizure cluster (which may simply be first signs of a seizure in some patients). The ability to respond adequately to a cluster may be compromised if appropriate action is not taken during any of these phases. The success of seizure action plans rests on patients' and caregivers' learning about and accepting the need to treat seizures acutely. Samples of seizure action plans are included in Appendix A.

The importance of patient awareness of seizure cluster risks and treatment benefits was highlighted in Penovich and colleagues' recent study involving adult patients with seizure clusters (n = 259), caregivers (n = 263), and clinicians (n = 339) [18]. Only a minority of patients (20%) reported that they would take a rescue medication in response to an emergent seizure cluster. Similarly, in a much earlier study by Tatum, survey responses from 76 adult patients with intractable epilepsy revealed that while two-thirds of respondents considered diazepam rectal gel a good treatment option and were not embarrassed by its use, 13% thought their ongoing breakthrough seizures were not sufficiently serious to warrant rescue treatment [19]. The study by Penovich et al. also illustrated the need to bridge communication gaps

Table 1
Studies of prevalence of seizure clusters.

Study	Population	N	Definition of seizure clusters	Prevalence
Haut et al., 2005 [13]	Patients treated at epilepsy monitoring unit and neurology clinic	141	≥3 seizures within 24 h	29% at baseline
Sillanpää & Schmidt, 2008 [14]	37-Year follow-up of 245 patients (≤15 years old) treated at hospital epilepsy clinic, 1961–1964	120	≥3 seizures within 24 h	22%
Martinez et al., 2009 [59]	Patients with records in General Practice Research Database, a United Kingdom-wide repository	2,936,279	≥3 seizures within ~24 h[a]	Epilepsy: 6.7/1000[b] (95% CI, 6.6–6.8) Seizure clusters: 2.5/10,000[b] (95% CI, 2.3–2.7)
Asadi-Pooya et al., 2016 [16]	Presurgical patients with drug-resistant focal epilepsy who underwent epilepsy surgery, 1986–2015	978 TLE: n = 681 ETLE: n = 83 Other: n = 214[c]	≥2 seizures within 2 days (before surgery)	TLE: 23.6% ETLE: 16.9%
Chen et al., 2017 [15]	Outpatients (≥16 years old) treated at comprehensive epilepsy centers with ≥1-year follow-up, 2005–2015	4116	≥3 seizures within 24 h, *or* ≥3× daily average (patients with daily seizures), *or* Determined by treating clinician	Overall: 14.9% Focal epilepsy: 16.3% IGE: 7.4% SGE: 27.1%
Detyniecki et al., 2018 [6]	Outpatients (≥12 years old) treated at comprehensive epilepsy center; prospective study with 1-year follow-up	247	≥2 seizures within 6 h	29% Active epilepsy (≥1 seizure within prior year): 46%

CI, confidence interval; ETLE, extratemporal lobe epilepsy; IGE, idiopathic generalized epilepsy; SGE, symptomatic generalized epilepsy; TLE, temporal lobe epilepsy.
[a] Seizure definition included some flexibility, especially with respect to time window for multiple seizures.
[b] Age-adjusted prevalence estimate.
[c] Patients classified as other, including those undergoing corpus callosotomy, vagus nerve stimulation, or multilobar resections, were included in analysis in both groups (TLE, ETLE).

between participating stakeholders; although 52% of clinicians reported a majority of their patients had a seizure action plan in place, only 30% of patients reported having one [18]. According to a survey of 100 families that included children with epilepsy, 87% had received a prescription for a rescue medication, but only 45% had a seizure action plan, and only 61% of those with a rescue medication prescription had received training on its use and administration [20].

Other studies have documented low prescribing rates and low usage rates for rescue medication for the treatment of seizure clusters. As reported in a retrospective study of adult patients with epilepsy (N = 4116), only 44% of those with a history of seizure clusters had received a prescription for a rescue medication [15]. A prospective study of seizure clusters (N = 247) found that only 28% of 72 patients in the highest risk group had a rescue medication prescription [6]. Finally, a study of European pediatric patients with prolonged seizures (N = 286) found that, though most had a prescription for a rescue medication, about 25% of the study population had not received rescue treatment [21].

3.2. Undertreatment in educational settings

Ensuring adequate rescue treatment of pediatric patients in educational settings is challenging, primarily because responsibilities for medication administration fall on school faculty. It is not surprising that low rates of adequate rescue treatment of pediatric patients with prolonged seizures/seizure clusters have been reported for the school environment [22]. Several investigators have summarized current and emerging rescue therapies and treatment guidelines in an effort to improve disease knowledge and the rates and effectiveness of treatment provided by school nurses and teachers [22–24]. Training programs covering the use and administration of rescue medication may increase the confidence and reduce administration errors among school personnel responsible for intervention [25]. More convenient (e.g., nasal rather than rectal) formulations should also improve the situation in schools, group homes, nursing homes, prisons, and other settings.

3.3. Current treatment landscape

The Epilepsy Foundation of America is actively working to develop consensus on best practices for rescue therapies, with input from all types of stakeholders—clinicians, patients, families, educators, pharmacists, school nurses, paramedics, and others—but at present, published guidelines do not exist. As a result, many patients at risk for seizure clusters lack a specific plan of action for emergent seizure clusters [18]. Results from a recent observational study showed that only 28% of patients with a recent history of seizure clusters had a rescue medication prescription, and the most frequently prescribed medication for rescue was oral lorazepam [6].

Characteristics of an ideal rescue treatment for seizure clusters include rapid onset of efficacy across a range of seizure types, rapid bioavailability at therapeutic levels with consistent patient-to-patient pharmacokinetics, portability and ease of preparation/administration, sustained activity to prevent seizure recurrence, availability in adult and pediatric dosing formulations, extended shelf life at ambient temperatures, low abuse potential, and a favorable adverse event profile [5,26]. Pharmacologic treatment in the management of seizure clusters is currently based on benzodiazepines, which generally are well-tolerated in this setting [3,7]. Commonly reported adverse events associated with benzodiazepines include lethargy, somnolence, and, rarely, respiratory depression, and intravenous (IV) and rectal administration of benzodiazepines has been associated with higher rates of respiratory adverse events in some but not all studies [27,28].

Until late 2019, diazepam rectal gel was the only US FDA-approved treatment for bouts of increased seizure activity in patients with epilepsy [27,29–31]. In clinical practice, however, oral alternatives (e.g., lorazepam) are often prescribed for acute rescue administration, especially in teenagers and adults, in whom rectal medications are highly unpopular [6]. Table 2 summarizes findings from prospective controlled studies of benzodiazepines used in various dosage forms for the acute

Table 2
Prospective controlled studies of benzodiazepines for acute treatment of seizures/seizure clusters.

Study	Administration route	Comparator	Subjects/group size	Primary assessment	Primary outcome result	Secondary/other results
Head-to-head studies of different benzodiazepine molecules						
Baysun et al., 2005 [45]	DZP-RG	MDZ-Bu	43 pediatric patients (age, 2 mo–12 y) presenting with seizures Initial treatment MDZ-Bu in group 1 and DZP-RG in group 2; if no response within 10 min, alternate drug administered	Prolonged convulsive seizures	Similar initial response (seizure cessation) DZP-RG: 85% MDZ-Bu: 78% ($P > 0.05$)	Agents had similar response times; seizure cessation within 5 min in >80% of patients ($P > 0.05$)
Bhattacharyya et al., 2006 [37]	DZP-RG	MDZ-IN	46 pediatric patients (age, 3 mo–12 y) 188 seizure episodes treated DZP-RG: n = 96 MDZ-IN: n = 92	Acute seizures of all types	Similar rates of seizure cessation at 10 min DZP-RG: 89% MDZ-IN: 97%	Respiratory rate and oxygen saturation significantly lower with DZP-RG vs MDZ-IN ($P < 0.05$) Time from drug administration to seizure cessation significantly shorter with MDZ-IN vs DZP-RG (117 vs 179 s; $P = 0.005$)
Fisgin et al., 2002 [39]	DZP-RG	MDZ-NS	45 children (age, 1–13 y) presenting with acute seizures (all types) Initial treatment with DZP-RG on odd days (n = 22) and MDZ-NS on even days (n = 23); if no response within 10 min, alternate drug administered	Acute convulsive seizures	Patients with seizure cessation within 10 min DZP-RG: 59% MDZ-NS: 87% ($P < 0.05$)	Time to seizure termination DZP-RG: 32% (2–5 min) MDZ-NS: 39% (1–2 min)
Holsti et al., 2007 [60]	DZP-RG	MDZ-IN	57 pediatric patients (age, <18 y) DZP-RG: n = 18 MDZ-IN: n = 39 Comparison of EMS-administered MDZ-IN vs historical DZP-RG controls	Prolonged seizures in prehospital setting	Patients treated with MDZ-IN vs DZP-RG were significantly less likely to experience seizures in ED, be admitted to hospital, and require intubation (multivariate analysis)	Treatment with MDZ-IN vs DZP-RG significantly reduced risk for PICU admission and need for anticonvulsant treatment in ED
Holsti et al., 2010 [38]	DZP-RG	MDZ-IN	92 pediatric patients (age, <18 y) DZP-RG: n = 42 MDZ-IN: n = 50 Comparison of MDZ-IN vs DZP-RG for in-home rescue use	Home-setting acute seizures requiring rescue treatment	Trend for reduced time to seizure cessation with MDZ-IN vs DZP-RG (median, 3.0 vs 4.3 min; $P = 0.09$)	Similar total seizure time with MDZ-IN vs DZP-RG (median, 10.5 vs 12.5 min; $P = 0.25$) No other significant between-groups differences in secondary endpoints
McIntyre et al., 2005 [41]	DZP-RG	MDZ-Bu	177 pediatric patients (age, 7 mo–15 y) presenting with acute seizures DZP-RG: n = 85 (110 seizures) MDZ-Bu: n = 92 (109 seizures)	Acute seizures	Higher rate of primary outcome "therapeutic success" (seizure cessation within 10 min, no respiratory depression, no recurrent seizure within 1 h) with MDZ-Bu vs DZP-RG (56% vs 27%; $P < 0.001$)	Median time from treatment to seizure cessation shorter with MDZ-Bu vs DZP-RG (8 vs 15 min; $P = 0.01$)
Mpimbaza et al., 2008 [61]	DZP-RG	MDZ-Bu	330 pediatric patients (3 mo–12 y) presenting with prolonged seizures in health clinic in Uganda DZP-RG: n = 165 MDZ-Bu: n = 165 Most patients had malaria, so many seizures were associated with fever	Prolonged seizures	Rate of treatment failure (no seizure cessation within 10 min or recurrent seizure within 1 h) higher with DZP-RG vs MDZ-Bu (43% vs 30%; $P = 0.016$)	Treatment failure rates similar in patients with malaria DZP-RG: 36% MDZ-Bu: 32% ($P = 0.534$) Much higher with DZP-RG in patients without malaria DZP-RG: 56% MDZ-Bu: 27% ($P = 0.002$)
Ashrafi et al., 2010 [42]	DZP-RS	MDZ-Bu	98 pediatric patients (age, 3 mo–12 y) with seizures lasting >5 min (or ongoing on ED arrival) DZP-RS: n = 49 MDZ-Bu: n = 49	Acute prolonged convulsive seizures	Proportion with seizure cessation at 4 min DZP-RS: 49% MDZ-Bu: 88% 5 min DZP-RS: 82% MDZ-Bu: 100%	Time to administration within 2 min DZP-RS patients: 22% MDZ-Bu patients: 82% 3 min DZP-RS patients: 90% MDZ-Bu patients: 94%

Table 2 (*continued*)

Study	Administration route	Comparator	Subjects/group size	Primary assessment	Primary outcome result	Secondary/other results
					8 min DZP-RS: 100%	Parent satisfaction with treatment/route DZP-RS: 14% MDZ-Bu: 94%
de Haan et al., 2010 [40]	DZP-RS	MDZ-NS	21 adults with intractable epilepsy and ≥10 exacerbations/year requiring rescue treatment	Seizure exacerbations requiring rescue treatment	Similar rates of seizure cessation within 15 min DZP-RS: 56/63 (89%) MDZ-NS: 50/61 (82%) (P = NS)	Similar mean time (min) to seizure cessation DZP-RS: 4.3 MDZ-NS: 4.6 Both agents well tolerated (similar AE rates) Caregivers/patients preferred convenience of MDZ-NS
Malu et al., 2014 [62]	DZP-RS	LZP-SL (1 mg or 2.5 mg dissolving tablet)	436 pediatric patients (age, 5 mo–10 y) presenting with seizures lasting >5 min, sub-Saharan Africa DZP-RS: n = 202 LZP-SL: n = 234	Prolonged convulsive seizures	Seizure cessation significantly faster with DZP-RS Proportion with cessation within 5 min DZP-RS: 38% LZP-SL: 28% 10 min DZP-RS: 79% LZP-SL: 56% 20 min DZP-RS: 91% LZP-SL: 83% (P = 0.012)	Seizure recurrence within 24 h DZP-RS: 39% LZP-SL: 36% (P = 0.481)
Nakken & Lossius, 2011 [43]	DZP-RS	MDZ-Bu	Adult patients with convulsive or nonconvulsive serial seizures/status epilepticus at residential epilepsy center DZP-RS: n = 18 (37 seizures) MDZ-Bu: n = 16 (43 episodes)	Serial seizures or status epilepticus	Similar rates of treatment success (seizure cessation within 10 min, no recurrence within 2 h) DZP-RS: 83.3% MDZ-Bu: 74.4% (P = NS)	Mean time to seizure cessation similar with DZP-RS vs MDZ-Bu for all seizure types except convulsive status epilepticus (5.0 vs 2.8 min; P = 0.012) MDZ-Bu preferred by all unit nurses and 6/7 patients who received both treatments
Scott et al., 1999 [44]	DZP-RS	MDZ-Bu	Pediatric patients with prolonged (>5 min) seizures at residential epilepsy center DZP-RS: n = 14 (39 seizures) MDZ-Bu: n = 14 (40 seizures)	Prolonged seizures	Similar rates of response (seizure cessation within 10 min after treatment) DZP-RS: 59% MDZ-Bu: 75% (P = 0.16)	Similar median time to seizure cessation with DZP-RS vs MDZ-Bu (8 vs 6 min; P = 0.31) Similar response rate and time to cessation for first treatment with each drug (9 pairs)
Ivaturi et al., 2009 [63]	DZP-IN	MDZ-IN DZP-IV and MDZ-IV also evaluated	3 healthy female volunteers (age, 20–24 y) 4-way study	PK	Mean t_{max} (min) DZP-IN: 28.8 MDZ-IN: 21.6 Mean C_{max} (ng/mL) DZP-IN: 179.2 MDZ-IN: 62.8	Nasal pain (maximum, 3.2/10; mean, 1.2 at 15 min) with both DZP-IN and MDZ-IN; nasal drainage and watery eyes with both
Lahat et al., 2000 [32]	DZP-IV	MDZ-IN	44 children presenting with febrile seizures in ED DZP-IV: n = 23 (26 seizures) MDZ-IN: n = 21 (26 seizures)	Prolonged febrile seizures	Mean time from ED arrival to seizure cessation significantly shorter with MDZ-IN vs DZP-IV (6.1 vs 8.0 min; P < 0.001)	Most of time difference from ED arrival to seizure cessation attributable to less time from arrival to treatment with MDZ-IN vs DZP-IV (3.5 vs 5.5 min); time from treatment to seizure cessation shorter with DZP-IV vs MDZ-IN (2.5 vs 3.1 min); P < 0.001 for both
Mahmoudian & Zadeh, 2004 [33]	DZP-IV	MDZ-IN	70 pediatric patients (age, 2 mo–15 y) presenting with acute seizures DZP-IV: n = 35 MDZ-IN: n = 35	Acute seizures	In both groups, all seizures controlled within 10 min; less mean time from administration to seizure cessation with DZP-IV vs MDZ-IN (2.94 vs 3.58 min; P = 0.007)	Reduced time from seizure onset to treatment initiation with MDZ-IN vs DZP-IV
Talukdar & Chakrabarty, 2009 [34]	DZP-IV	MDZ-Bu	120 pediatric patients presenting with convulsive seizures in ED DZP-IV: n = 60 MDZ-Bu: n = 60	Convulsive seizures	Similar rates of response (cessation of all motor activity within 5 min) DZP-IV: 93% MDZ-Bu: 85% (P = 0.14)	Total mean response time (seizure initiation to cessation) significantly shorter with DZP-IV vs MDZ-Bu (2.39 vs 2.98 min; P = 0.004) Time to treatment longer with

(*continued on next page*)

Table 2 (*continued*)

Study	Administration route	Comparator	Subjects/group size	Primary assessment	Primary outcome result	Secondary/other results
						DZP-IV Time from treatment to cessation longer with MDZ-Bu
Thakker & Shanbag, 2013 [35]	DZP-IV	MDZ-IN	50 pediatric patients presenting with convulsive seizures lasting >10 min in ED DZP-IV: n = 23 MDZ-IN: n = 27	Acute seizures	Similar rates of response (seizure cessation within 10 min) DZP-IV: 65% MDZ-IN: 67% ($P > 0.05$)	Significantly longer mean time from hospital arrival to seizure cessation with DZP-IV vs MDZ-IN (17.2 vs 6.7 min) attributable to delayed initiation of treatment (time from treatment to response shorter with DZP-IV: 2.7 vs 3.0 min)
Ahmad et al., 2006 [64]	LZP-IN	PDH-IM	160 pediatric patients (age, 2 mo–12 y) presenting with seizures lasting >5 min in Malawi LZP-IN: n = 80 PDH-IM: n = 80	Acute seizures	Trend toward more seizure cessation within 10 min with LZP-IN vs PDH-IM (75% vs 61%; $P = 0.06$)	Proportion needing ≥2 rescue treatments LZP-IN: 10% PDH-IM: 26% ($P = 0.007$) Proportion with recurrent seizure within 24 h LZP-IN: 10% PDH-IM: 14% ($P = 0.46$)
Diazepam (DZP) studies						
Cereghino et al., 2002 [65]	DZP-RG	Placebo	70 adults with ARS DZP-RG: n = 31 Placebo: n = 39 Pooled analysis of 2 studies	ARS	Fewer seizures/h with DZP-RG vs placebo within 12-h postdose period (median, 0.00 vs 0.13; $P = 0.002$)	Significantly more seizure-free patients with DZP-RG vs placebo (71% vs 28%; $P = 0.001$) Kaplan–Meier analysis of time to next seizure favored DZP-RG ($P < 0.001$)
Dreifuss, 1998 [66]	DZP-RG	Placebo	125 patients (age, 2–60 y) with ≥4 ARS episodes within previous year and ≥1 within previous 3 mo	ARS	Significantly lower median seizure frequency/h with DZP-RG (0) vs placebo (0.3) ($P < 0.001$)	DZP-RG associated with significant improvement vs placebo in caregiver global assessment of treatment outcome ($P < 0.001$)
Kriel et al., 1999 [67]	DZP-RG	Placebo	133 children (age, 2–17 y) with ARS DZP-RG: n = 68 Placebo: n = 65 Pooled analysis of 2 studies of similar design	ARS	Significantly fewer seizures/h with DZP-RG vs placebo (median, 0.0 vs 0.25; $P < 0.001$)	Significantly more seizure-free patients at 12 h with DZP-RG vs placebo (59% vs 31%; $P = 0.001$) Time to next seizure (Kaplan–Meier analysis) significantly longer with DZP-RG ($P = 0.0002$)
Chiang et al., 2011 [68]	DZP-RS	DZP-IV administered rectally	24 children (age, 2–18 y) with intractable epilepsy Seizures treated with DZP-IV for 3 mo, then DZP-RS for 3 mo	Acute seizures	Seizure cessation within 10 min of first dose DZP-RS: 90/103 (87%) DZP-IV: 103/127 (81%) (P = NS)	Seizure cessation within 10 min of second dose DZP-RS: 12/13 (92%) DZP-IV: 21/24 (88%) No significant differences between treatments on any measure All agents well tolerated
Agarwal et al., 2013 [69]	DZP-IN (2 formulations)	DZP-IV	24 3-way crossover study; all subjects received each medication with washout between treatment periods	PK	$AUC_{0-\infty}$ (ng*h/mL) DZP-IN suspension: 5381 DZP-IN solution: 7338 DZP-IV: 4104 t_{max} (h) DZP-IN suspension: 1.0 DZP-IN solution: 1.5	Subjects (n) with AEs DZP-IN suspension: 9 DZP-IN solution: 8 DZP-IV: 10 All AEs mild to moderate
Gizurarson et al.,1999 [70]	DZP-IN	DZP-IV	9 healthy volunteers Crossover PK study with low doses (2 mg each dosage form)	PK	Mean (SD) DZP-IN t_{max}: 18 (11) min	Mean (SD) DZP-IN C_{max} at 18 min (mean t_{max}) was 33% (22%) vs DZP-IV at 10 min postdose
Henney et al., 2014 [53]	DZP-IN (5 mg, 20 mg)	DZP-RG (20 mg)	24 healthy volunteers Crossover PK study for all 3 treatments	PK	Mean (SD) C_{max} DZP-IN 5 mg: 96 (28) ng/mL DZP-IN 20 mg: 350 (103) ng/mL DZP-RG 20 mg: 352 (93) ng/mL Median t_{max} 1.0 h, 1.0 h, 1.5 h, respectively	Bioavailability similar across dosage forms DZP-IN exhibits linear PK
Ivaturi et al., 2013 [71]	DZP-IN 3 different formulations Nas-A 10 mg	DZP-RG	12 healthy volunteers 4-way crossover study	PK	Median t_{max} 0.75 h for all 4 treatment types Mean C_{max} (ng/mL) Nas-A 10 mg: 181.8	Mean maximal pain scores (scale, 0–10) Nas-A 10 mg: 2.6 Nas-B 10 mg: 1.6

Table 2 (*continued*)

Study	Administration route	Comparator	Subjects/group size	Primary assessment	Primary outcome result	Secondary/other results
	Nas-B 10 mg Nas-B 13.4 mg				Nas-B 10 mg: 151.3 Nas-B 13.4 mg: 180.7 DZP-RG: 160.9	Nas-B 13.4 mg: 1.4 DZP-RG: 0.3
Abou-Khalil et al., 2013 [67,72]	DZP-IM (auto-injector)	Placebo	DZP-IM: n = 82 Placebo: n = 81	ARS	Mean time to next seizure or rescue reduced with DZP-IM vs placebo HR for next event: 0.55 (95% CI, 0.34–0.88; $P = 0.012$)	Reduced rates of rescue medication use and ED visits with DZP-IM
Lorazepam (LZP) studies						
Arya et al., 2011 [36]	LZP-IN	LZP-IV	141 pediatric patients (age, 6–14 y) presenting with convulsive seizures LZP-IN: n = 71 LZP-IV: n = 70	Acute seizures	Similar rates of seizure cessation within 10 min LZP-IN: 83% LZP-IV: 80% ($P = 0.635$)	Similar rates of nonrecurrence within 1 h LZP-IN: 62% LZP-IV: 59% ($P = 0.680$) Median time to seizure cessation: 3 min in both groups ($P = 0.900$) Noninferiority study: LZP-IN judged not inferior to LZP-IV
Alprazolam (ALZ) studies						
French et al., 2019 [58]	ALZ-IP (Staccato aerosolization pulmonary delivery system)	Placebo	5 adults with epilepsy and PPR (induction of epileptiform EEG with light flashes at varying standard frequencies)	PPR	Significantly lower induced PPR activity at 2 min with ALZ-IP vs placebo at all tested doses (0.5, 1.0, 2.0 mg)	Both ALZ-IP efficacy response (degree of PPR suppression) and side effect response (sedation) were dose related Approximately linear PK of Staccato ALZ-IP over tested dose range

AE, adverse event; ALZ-IP, intrapulmonary alprazolam; ARS, acute repetitive seizures; $AUC_{0-\infty}$, area under the curve from time zero to infinity; C_{max}, maximum serum concentration; DZP-IM, intramuscular diazepam; DZP-IN, intranasal diazepam; DZP-IV, intravenous diazepam; DZP-RG, diazepam rectal gel; DZP-RS, diazepam rectal solution; ED, emergency department; EEG, electroencephalogram; EMS, emergency medical services; HR, hazard ratio; LZP-IN, intranasal lorazepam; LZP-IV, intravenous lorazepam; LZP-SL, sublingual lorazepam; MDZ-Bu, buccal midazolam; MDZ-IN, intranasal midazolam; MDZ-IV, intravenous midazolam; MDZ-NS, midazolam nasal spray; NS, nonsignificant; PDH-IM, intramuscular paraldehyde; PICU, pediatric intensive care unit; PK, pharmacokinetics; PPR, photoparoxysmal response; SD, standard deviation; t_{max}, time to maximum plasma concentration.

treatment of seizures and seizure clusters. Only a few of these studies specifically assessed the treatment of seizure clusters; most involved treatment of emergent convulsive seizures of any etiology. Many also focused on the use of preparations obtained from hospital or compounding pharmacies, because the only commercially available approved therapies for seizure clusters at the time the studies were conducted were diazepam rectal gel and buccal midazolam, the latter used only in the European Union. Nevertheless, results from most of the studies of rectal, buccal, or intranasal benzodiazepine formulations showed reasonable efficacy, equal to or better than that of IV or rectal formulations, with seizures ceasing within 10 min in the majority of patients. Studies evaluating IV formulations (diazepam [32–35] or lorazepam [36]) have consistently reported the shortest mean or median time from drug administration to seizure cessation (within 3 min; Table 2). Studies of nasal formulations of midazolam [32,33,35,37–40] or lorazepam [36] have also reported relatively rapid treatment effects for aborting seizures (reported seizure cessation within about 1 to 5 min across studies). Reported times to seizure cessation across studies of buccal formulations of midazolam range from about 3 min to 8 min [34,41–45], while times to cessation in rectally administered diazepam have been more variable across studies, ranging from 2 to 15 min [37–45]. Outside the hospital or epilepsy specialty practice environment, it is essential that pharmacologic treatment modalities be designed to provide user-friendly intervention across multiple settings.

3.4. Emerging approaches to acute therapy for seizure clusters

Given the reliance on benzodiazepines as rescue treatment for seizure clusters, it is unclear if traditional AEDs (e.g., phenytoin/fosphenytoin, valproate/valproic acid, levetiracetam, carbamazepine) can play a role as rescue therapies. Despite efforts to develop formulations suitable for rescue use, such agents have yet to demonstrate the bioavailability/absorption characteristics required for intramuscular or rectal administration [46]. However, because benzodiazepines rapidly redistribute to fatty tissues after stopping seizures, traditional longer acting AEDs may be administered orally after successful rescue treatment, with seizure cessation and return to full alertness, to prevent recurrent seizures [5].

Most recent efforts around the development of rescue medications have focused on the route of administration, with key factors being portability, ease of use, rapidity of effect, and their ability to abort seizure clusters, usually by preventing the occurrence of further seizures within the cluster. The most heavily investigated routes include rectal, intramuscular, buccal, sublingual, oral, and intranasal; other potentially useful routes are subcutaneous and intrapulmonary [5,26,47–50]. Intravenous administration is reserved for medical settings with qualified personnel [27].

Factors reported to have the greatest impact on choice of administration route include the surface area available for drug absorption, the blood flow across the absorptive surface, and the lipophilicity of the treatment agent—the greater the better for all three [26]. In general, greater drug lipophilicity is associated with more rapid absorption but poorer solubility in aqueous solutions. Each potential administration route is associated with one or more possible drawbacks and advantages (Table 3) [3,5,26,51].

Intranasal formulations of midazolam and diazepam were recently approved [30,31,50,52–54], and a buccal formulation of midazolam has been available in Europe since 2011 [55]. Other formulations being developed for rescue treatment of seizure clusters include [52–54] diazepam buccal film [48,56,57] and alprazolam for inhalation [7,58].

Table 3
Potential drawbacks and advantages for rescue medication administration routes [3,5,26,51].

Administration route	Potential drawbacks	Potential advantages
Oral	• Delayed absorption/bioavailability • Aspiration • Patient difficulty/refusal and need for cooperation	• Patient/caregiver convenience and familiarity • Low cost
Buccal/sublingual	• Aspiration (for liquids) • Inaccessibility (if seizure involves oral area)	• Can be rapidly administered and absorbed
Intranasal	• Variable absorption (based on secretions/mucus load) • Reactive secretions (possible aspiration risk) • Nasal irritation/pain	• Can be rapidly administered and absorbed
Inhaled/intrapulmonary	• Possibly variable absorption • Possible need for patient cooperation	• Minimal dose-preparation needed • May allow use of relatively small doses • More rapid drug absorption than other parenteral routes
Intramuscular	• Risk of abscess • Discomfort • Use of needle	• Can be rapidly administered • Reliable absorption
Rectal	• Socially unacceptable in many settings • Potential problem for unrelated caregivers • Slow administration, especially in older and clothed patients • Possibly variable absorption	• Widely used and well-studied • Rapidly absorbed
Intravenous	• Difficult to administer (requires substantial medical expertise) • Setup time	• Very rapid effect • High bioavailability • Optimal route in hospital settings

4. Summary

Establishment of an accepted consensus definition of seizure clusters is perhaps the most urgent need regarding seizure clusters and their management. As with many initially ill-defined clinical scenarios or conditions, further study of seizure clusters may identify multiple subtypes and etiologies that require distinct management strategies. It is possible that management of seizure clusters may require highly individualized treatment plans based on general guidelines for initial treatment selection, followed by empirical evaluation of available agents. Until seizure clusters are more comprehensively recognized as an important clinical phenomenon, the development of effective and safe management strategies and new treatment agents will be hindered.

A surprisingly large proportion of patients with epilepsy do not have an action plan in place, and many have not received a prescription medication for seizure rescue. Two sample seizure action plans appear in Appendix A. One is a generalized plan, and the other was developed for school use. Ideally, a seizure action plan should be developed collaboratively by patients and their physicians, and shared with appropriate personnel at school, worksite, group home, or other settings.

Initiating and continuing development of pharmacologic treatment options across a range of administration routes is essential. As it is highly unlikely that any single medication or delivery system will suit all patients, multiple therapeutic options are needed so that the most appropriate agent(s) can be selected for each individual patient.

When the disease course of seizure clusters and the risk factors for their development are more fully understood, it may be possible to pursue prophylactic treatment approaches to reduce the risk for seizure clusters and, though outside the scope of this discussion, even the risk for seizures of any type. There has been inadequate study of the potential for progression from seizure clusters to status epilepticus or sudden unexpected death in epilepsy, but the risk is certainly not zero. There has been almost no investigation of the extent of long-lasting or permanent harm from seizure clusters to either brain function or seizure diathesis. The hope is that the latest effective and more convenient rescue therapies—those recently approved and those to come—will help expedite these investigations, decrease the occurrence of status epilepticus and ED visits, and improve quality of life for patients with seizure clusters.

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Appendix A. Sample seizure action plans

Epilepsy Foundation of America, Inc.

Two-page plan for general use. https://www.epilepsy.com/sites/core/files/atoms/files/GENERAL%20Seizure%20Action%20Plan%202020-April7_FILLABLE.pdf

Accessed May 20, 2020.

American Academy of Pediatrics

Four-page plan for school submission/use.

https://www.aap.org/en-us/Documents/Seizure_Action_Plan_for%20School.pdf

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