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The unmet need for rapid epileptic seizure termination (REST)

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ABSTRACT

Approximately 40% of epilepsy patients will continue to experience breakthrough seizures despite stable antiepileptic drug regimens. Rescue treatments have demonstrated efficacy and safety for select seizure emergencies. Outpatient administered intranasal and rectally delivered medications are regulatory approved for acute repetitive seizures (ARS), and injectable benzodiazepines are indicated for parenteral treatment of established status epilepticus. Despite these advances, no studies have been shown to abort an ongoing seizure following patient or caregiver home administration of therapy at the first clinical sign of seizure onset. Such treatment would require rapid systemic absorption without intravenous access, and evidence of seizure cessation within minutes of administration that is superior to placebo (eg, seizure self-regulation). Rapid epileptic seizure termination (REST) treatment may apply to multiple seizure emergencies beyond ARS, including focal or generalized seizures preceded by an aura, flurries of absence or myoclonic seizures, or prolonged focal and generalized seizures at high risk of progression to status epilepticus. Novel investigational drug delivery systems have demonstrated feasibility of intraictal delivery and seizure cessation by two minutes. Ongoing randomized trials of REST treatment for diverse seizure emergencies hold the potential to decrease bouts of mental and physical incapacitation in patients with drug-resistant epilepsy.

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1. Introduction

Epilepsy is one of the most common diseases of the central nervous system and uncontrolled epileptic seizures have a negative impact on patient quality of life, increasing risk of injury, death and socioeconomic disadvantage [1–3]. Many patients (60–70%) achieve long-term seizure freedom with titration of a daily multitherapy antiseizure medication (ASM) regimen. However, it is estimated that up to 40% of newly diagnosed epilepsy patients will continue to experience resistant breakthrough seizures despite stable ASM therapy [4].

There are various phenotypes of seizure emergencies, each of which may present an increased risk for injury, seizure recurrence, progression to status epilepticus, and/or mortality [5–7]. Rescue treatments for two specific seizure emergencies, acute repetitive seizures (ARS) and established status epilepticus, have been systematically studied and are available for clinical use. The ARS therapies may be administered postictally in the outpatient setting upon recognition of cluster seizures and have been shown to prevent or delay subsequent recurrent seizures [8–10]. Status epilepticus is a guideline-classified neurologic emergency [11]. Acute medical treatment of status epilepticus is generally administered intravenously, and warrants hospitalization for stabilization and reduction of the risk for irreversible neuronal damage [12,13].

There are no Food and Drug Administration (FDA) approved treatments for the rapid termination of an ongoing seizure that has not progressed to status epilepticus. Demonstration of a rapid epileptic seizure termination (REST) treatment that acts within minutes of outpatient administration by the patient or a caregiver could advance the care of epilepsy and improve patient outcomes [14,15].

2. Types of seizure emergencies

2.1. Operational seizure classification

The International League Against Epilepsy (ILAE) developed a revised operational classification of seizure types in 2017 according to onset (focal or generalized), and the practical consideration of patient awareness [16]. Focal aware, focal unaware and generalized seizures may be further characterized by motor or nonmotor manifestations, but regardless of the precision of subclassification, any unexpected breakthrough seizure in the setting of previously controlled epilepsy on stable ASM treatment is burdensome to the patient and presents risk for injury [17]. Seizure emergencies may result from any seizure type, but are typically realized when a single episode alludes self-regulatory mechanisms of spontaneous termination, or repetitive seizure episodes cluster temporally [18].

2.2. Categorizing seizure emergencies

Acute repetitive seizures (ARS), although not uniformly accepted, is a clinically defined syndrome characterized by multiple breakthrough seizures (at least two), generally occurring over a period of six to 24 hours in a distinctive pattern [6]. The goal of ARS treatment is to stop the cycle of seizure clusters, delaying or preventing the next seizure, once the pattern is recognized. Seizure clusters may increase the risk of neuronal death, particularly with decreasing interseizure intervals [7]. In contrast, status epilepticus is a clinical state in which a single, unremitting, prolonged seizure will not terminate spontaneously, ultimately leading to neuronal death and brain injury [5]. Documented status epilepticus, defined as greater than five minutes of tonic-clonic convulsions or 10 minutes duration of focal seizure activity, requires urgent intervention with parenteral anticonvulsive therapy and cardiopulmonary support [11,12]. In addition to ARS and status epilepticus, the spectrum of seizure emergencies includes a prolonged seizure that has not yet qualified as progression to status epilepticus, but has failed to self-terminate in a reasonably short time period [18]. How long is "too long" (eg, when is neuronal damage inevitable) to wait for spontaneous termination of a prolonged seizure remains undefined [5], beyond the established recommendation for acute treatment of status epilepticus. To this end, medical management of a single prolonged seizure that has not yet progressed to status epilepticus would require administration within a finite window of time and demonstration of rapid activity (less than five minutes from seizure onset to termination) to offer clinical benefit. Examples of seizure emergencies with current unmet medical need include focal or generalized seizures preceded by an aura, flurries of absence or myoclonic seizures, or prolonged focal and generalized seizures at high risk of progression to status epilepticus.

3. Regulatory approved seizure rescue treatments

3.1. FDA-approved rescue treatments for ARS

There are three FDA-approved medical treatments indicated for management of ARS in the outpatient clinical setting. Each agent was investigated in a relatively homogenous group of epilepsy patients with a documented history of qualifying recurrent seizure cluster episodes.

Diazepam rectal gel (Diastat®) is a rectally administered gel formulation of the benzodiazepine, diazepam, that has been shown to prevent or delay subsequent seizures in patients who experience seizure clusters or ARS. Clinical trials demonstrated that the frequency (per hour) of recurrent seizures was significantly reduced over a period of 12–24 hours following the onset of an identifiable seizure cluster and administration of Diastat versus placebo. Diastat controlled trials report that peak plasma concentration is reached in 90 minutes [8].

Diazepam nasal spray (Valtoco®) is an intranasally administered formulation of the benzodiazepine, diazepam, recently approved for the treatment of ARS in patients with epilepsy. Its clinical efficacy in this setting is based on demonstration of its relative bioavailability compared to diazepam rectal gel (Diastat) in healthy adults. Despite its intranasal administration, Valtoco, like Diastat, reaches peak plasma concentration in 90 minutes [9].

Midazolam nasal spray (Nayzilam®) is an intranasally administered formulation of the benzodiazepine, midazolam, also approved for the treatment of ARS in patients with epilepsy. Like Diastat, it has been shown to prevent or delay subsequent seizures in patients who experience seizure clusters or ARS. Clinical trials demonstrated that more patients treated with Nayzilam after the first cluster were free of seizure cluster activity at 10 minutes, and without recurrence up to 6 hours versus those receiving placebo [19]. Nayzilam reaches peak plasma concentration in 17.3 minutes [10].

3.2. Investigational rescue treatments for ARS

In addition to the FDA-approved rectal and nasally administered benzodiazepines, active studies are investigating a buccal soluble film formulation of diazepam for ARS [20]. Precedent for this administration method has been established by the commercial availability and FDA-approval of clobazam oral film (Sympazan™) as a daily adjunctive ASM for the treatment of seizures associated with Lenaux-Gastaut Syndrome [21]. Clobazam oral film has not been systematically developed for the treatment of ARS, but the investigational diazepam buccal film (Libervant™)

Table 1
FDA-approved seizure rescue treatments [8–10,13,23,38–40].

Approved Rescue Treatment	Indication	Route of Administration	Time to Peak Plasma Concentration (T_{max})*	Elimination half-life ($T_{1/2}$)**
Diazepam rectal gel (Diastat®) Valeant Pharmaceuticals	Management of selected, refractory, patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity.	Rectal	90 minutes	46 hours
Diazepam nasal spray (Valtoco®) Neurelis, Inc.	Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.	Nasal	90 minutes	49.2 hours
Midazolam nasal spray (Nayzilam®)UCB, Inc.	Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older.	Nasal	17.3 minutes	2.1–6.2 hours
Diazepam for injection	Treatment of status epilepticus	IM/IV	1–3 minutes	30–60 hours
Lorazepam for injection	Treatment of status epilepticus	IM/IV	1–3 minutes	14+/-5 hours
Midazolam for injection	Treatment of status epilepticus	IM	30 minutes	4.2+/-1.87 hours

IV, intravenous; IM, intramuscular
*Therapeutic levels and time to clinical effect may be achieved before T_{max}
**$T_{1/2}$ is an estimation of duration of effect

was recently shown to have similar periictal and interictal pharmacokinetics and time to peak plasma concentration relative to data reported with the approved rectal gel, Diastat [20]. Further, interim data from a safety, tolerability, and usability study of diazepam buccal film in patients requiring treatment for ARS or cluster seizures has been reported and supports its potential future application in this setting [22].

3.3. FDA-approved rescue treatments for status epilepticus

Injectable benzodiazepines (diazepam, lorazepam) are approved for the acute management of status epilepticus, and they are the currently recommended initial therapy of choice in the emergency treatment setting [13]. The parenteral intravenous administration of potent and short-acting benzodiazepines necessitates close medical monitoring for the occurrence of life-threatening hypotension, respiratory depression requiring intubation, cardiac arrythmias and other serious side effects. As such, intravenous benzodiazepines do not represent a formulation suitable for use outside of a medically controlled clinical setting. In the prehospital emergency medical services (EMS) treatment setting, paramedic administration of intramuscular midazolam (via autoinjector) has been shown to be noninferior to intravenous lorazepam in termination of status epilepticus, and may be a practical alternative prior to hospital arrival [23]. In practice, every effort to rapidly identify status epilepticus and/or avoid seizure progression to status epilepticus may reduce the resultant risk of hospital admission, and the potential for cardiac and respiratory complications, and brain injury [24].

A comparison of the indications, formulations, and pharmacokinetics of FDA-approved seizure rescue treatments is depicted in Table 1.

3.4. EMA-approved rescue treatment for pediatric prolonged, acute, convulsive seizures

In contrast to the United States, the only ARS rescue treatment approved in both children and adults in the European Union remains Diastat rectal gel. However, in 2011, oromucosal midazolam solution, Buccolam®, became the first pediatric-use marketing authorization approval (PUMA) by the European Medicines Agency (EMA) [25]. The PUMA was granted primarily based on comparable efficacy and safety of oromucosal midazolam to diazepam rectal gel, demonstrating cessation of visible signs of seizures within 10 minutes of administration into the buccal cavity. Maximum plasma concentrations of Buccolam are reached within 30 minutes in children [26].

4. Rapid epileptic seizure termination (REST) treatment

To date, none of the FDA-approved seizure rescue treatments have been systematically studied in epilepsy patients with a history of non-clustering but prolonged breakthrough seizures that, while not routinely progressing to status epilepticus, will evade self-termination for two minutes or longer. Such patients experience a reduced quality of life, adapting activities of daily living to accommodate potential unexpected episodes of physical and/or mental incapacitation. An effective and practical rapid epileptic seizure termination (REST) treatment would require the feasibility of noninvasive, peri- and/or intraictal outpatient administration, portability, ease of use, and pharmacokinetic properties equivalent to parenteral systemic absorption with acute onset anticonvulsive activity [14]. Rectally, intranasally and buccally administered commercially available benzodiazepines may not be suitable candidates for REST treatment due to their inability to reach peak plasma drug concentrations (T_{max}) during the window of opportunity for proactive seizure cessation. However, the pivotal ARS clinical trials evaluating the efficacy and safety of these rescue treatments did not address ongoing seizure termination, but rather the endpoint of prevention or delay of a subsequent seizure, as indicated by absence of seizure activity at 10 minutes and 6 hours post administration [8,10]. Drug absorption by mucosal routes of administration, such as the rectum, nasal or buccal cavity, is likely variable, and the precise onset of anticonvulsive activity is unknown. Thus, whether the seizure threshold is sufficiently elevated with rectally or intranasally administered diazepam or midazolam to enable early seizure termination at plasma levels below T_{max} remains a research question [27].

Approved treatments for status epilepticus, while generally delivered directly into the systemic circulation with onset of anticonvulsive action in one to three minutes, are not practical options for outpatient REST therapy because of the requirement for parenteral administration by medically trained professionals and their potential for acute toxicity [13,23].

4.1. Unmet need for REST treatment

Seizure duration varies by seizure type and individual patient anatomic and physiologic factors [28]. Further, a single patient may experience seizures of varying types and duration. However,

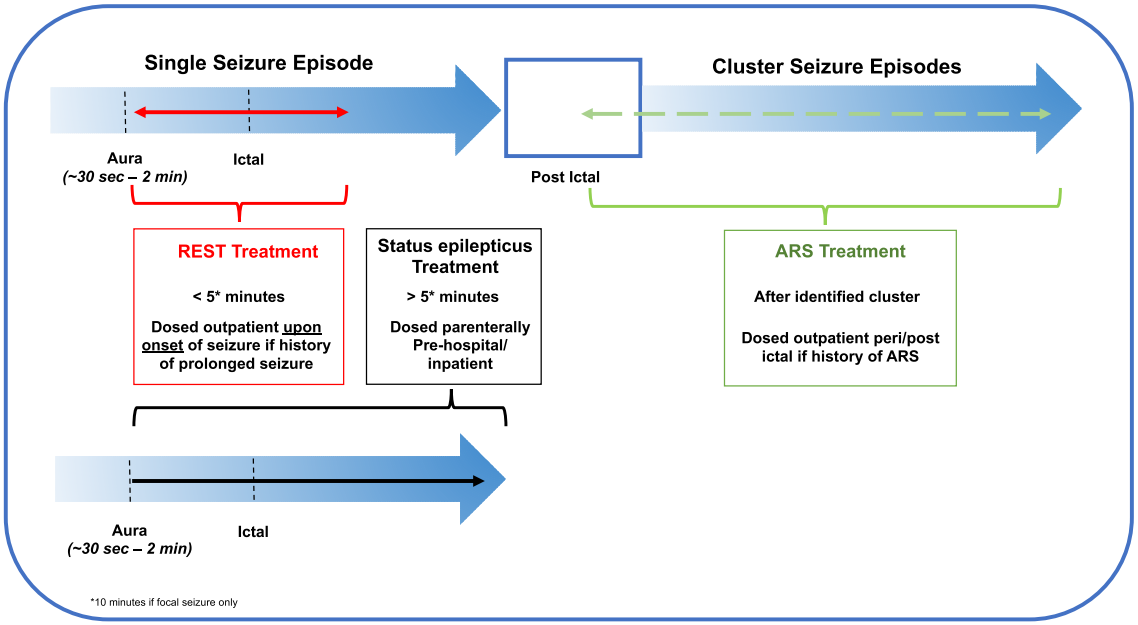

Fig. 1. Differential application of REST, status epilepticus, and ARS treatments.

Table 2
Investigational potential REST treatments [32,36,38].

Drug-delivery system description (Sponsor)	Method of administration	Time to REST effect	REST Evidence	Phase of development
Stacatto® alprazolam (Engage Therapeutics, a wholly owned subsidiary of UCB)	Oral inhalation of heated drug vapor	30 seconds* T_{max} = 2 minutes	• Abrogation of PPR • Seizure termination response > placebo	Phase 3 REST planned
Zeneo® midazolam (Crossject)	Needle-free transdermal injection of drug solution to muscle	3.3 minutes† T_{max} = NR	• Zeneo injection bioequivalence to IM product delivery	FDA orphan drug designation for status epilepticus
Midazolam autoinjector (Seizalam® Meridian Medical)	Intramuscular autoinjection of drug solution	3.3 minutes† T_{max} = 30 minutes	• Status epilepticus termination = IV lorazepam	Phase 3 status epilepticus completed

NR, not reported; PPR, photoparoxysmal response
*30 second mean time to seizure cessation in phase 2b across all responding seizure types
† Intramuscular (IM) midazolam median time from active treatment to cessation of convulsions [23,36]

despite the seemingly random pattern of breakthrough seizure occurrence, predictability may be learned through historical assessment of seizure onset, seizure location, seizure semiology, and clinical evolution of seizures [29]. As such, patients and caregivers are frequently able to identify predictable breakthrough seizure patterns in epilepsy, including triggers (menses, missed medications, alcohol, sleep deprivation), the presence and nature of auras, the tendency to cluster (eg, ARS episodes), as well as transitions in awareness and secondary generalization. ARS therapies have significantly advanced the field of seizure rescue treatment, and offer the potential for cognitive and physical recovery by 10 minutes following the first cluster seizure event and successful postictal dosing. However, given that significant seizure activity may occur in the first 10 minutes, and may not be preceded by an identifying cluster, fast-onset treatment options capable of rapidly terminating an evolving seizure if administered by the patient or caregiver at the first sign or symptom could extend rescue treatment to a broader epilepsy population (Fig. 1).

5. Potential REST treatments in clinical development

The clinical development of a viable REST treatment has focused on novel mechanisms for non-invasive delivery of established anticonvulsive medications (eg, benzodiazepines) into the systemic circulation in concentrations sufficient to rapidly abolish electroencephalogram (EEG) documented epileptiform activity [30]. Literature review and focused internet search suggests that at least three investigational drug delivery systems have the potential for REST treatment, Staccato® alprazolam, Zeneo® midazolam, and midazolam intramuscular autoinjector (Table 2).

5.1. Staccato alprazolam

Staccato alprazolam is an investigational, single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of alprazolam. Device actuation, formation of aerosol drug vapor, and delivery deep into the lung is accomplished with a single, normal breath. Initial pharmacokinetics of Staccato alprazolam in healthy participants demonstrated achievement of T_{max} within two minutes of administration and rapid onset of pharmacodynamic effects [31]. A phase 2a proof of concept study in adults with epilepsy and a history of photoparoxysmal response on EEG showed that a 2-mg dose of Staccato alprazolam terminated epileptiform activity by the first two-minute assessment in four of five treated patients, with continued effect through six hours [14]. Subsequently, a ran-

domized, multicenter, placebo-controlled, phase 2b trial evaluated the feasibility of self or caregiver administration, response rate (seizure activity cessation within two minutes after administration and no recurrence of seizure activity within two hours), and safety of two doses of Staccato alprazolam (1-mg and 2-mg) in 116 epilepsy patients with predictable seizure patterns, including generalized seizures starting with a flurry of absence or myoclonic seizures, prolonged focal seizures, or clusters of $\geq$ two seizures within two hours. Both doses of Staccato alprazolam demonstrated the ability to rapidly terminate seizures in two minutes or less, with response rates statistically superior to placebo (65.8% and 65.8% versus 42.5%, respectively; $p = 0.0158$ combined treatment arms versus placebo). Among responding patients treated with Staccato alprazolam, median time to seizure cessation was 30 seconds. The most common adverse events included somnolence (14.5%), cough (14.5%), dysgeusia (13.2%), dizziness (5.3%), sedation (2.6%), and throat irritation (2.6%). There were no treatment-related serious adverse events and the majority of reported events were mild in severity [32]. Based on the existing evidence of REST efficacy with Staccato alprazolam, a phase 3 outpatient study in patients with prolonged generalized, focal or cluster seizures is planned.

5.2. Zeneo midazolam

Zeneo (manufactured by Crossject, Dijon France) is a novel, prefilled needle-free, cartridge-based autoinjector device in development to deliver drugs, in one tenth of a second, through the skin surface to varying subdermal levels (intramuscularly, intradermally, subcutaneously) via gas propulsion and micronozzle array [33]. A human factors study conducted on healthy volunteers suggest the device can be correctly and effectively used by the average adult [34]. Pharmacokinetic studies comparing administration of drug product by the Zeneo delivery system or conventional needle and syringe have met bioequivalence criteria across multisite injections [35]. Zeneo midazolam received FDA Orphan Drug designation in 2018 for the treatment of status epilepticus, facilitating its development as a potential outpatient, REST medication [36]. Clinical data in patients with epilepsy demonstrating abortive efficacy in the treatment of prolonged seizures is awaited.

5.3. Intramuscular midazolam via autoinjector

Proof of concept for the successful clinical application of an intramuscular midazolam autoinjector as a REST treatment for adults and children in status epilepticus under the care of paramedics has been previously demonstrated [23]. Seizalam™ (intramuscular midazolam) was recently FDA-approved for healthcare professional administration and treatment of status epilepticus as a medical countermeasure for people exposed to chemicals that cause prolonged seizures, whether those situations are in combat, domestic accidents or international attack [37,38].

6. Conclusion

A substantial minority of patients continue to live with uncontrolled drug-resistant epilepsies. Advances in the acute treatment of breakthrough seizures have been made, but they remain applicable only to ARS/cluster seizures and status epilepticus [8–10,14]. There is clinical, economic, and social burden associated with breakthrough seizures [18]. The introduction of a REST treatment shown to cease epileptiform activity within minutes [15], that may be administered at home by the patient or a caregiver at the first clinical sign of an active or impending seizure, has the potential to significantly improve the lives of patients living with epilepsy. Integration and availability of ARS, status epilepticus, and REST medications may allow an individualized approach to the recommendation for rescue treatment according to patient presentation and type of seizure of emergency.

Finally, given the dearth of knowledge concerning the precise relationship between the pharmacocokinetics, pharmacodynamic and anticonvulsive onset of action of fast acting benzodiazepines, there remains opportunity to further investigate the approved intranasally administered ARS treatments, as well as other novel seizure rescue medication formulations (eg, buccal soluble film), as potential REST therapies. Evidence for REST efficacy will require appropriately designed clinical trials evaluating endpoints that accurately measure early termination of an ongoing, prolonged seizure that has not progressed to status epilepticus.

Declaration of Competing Interest

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