

Rethinking Seizure Emergencies



Inspired by **patients.**
Driven by **science.**

Objectives

- Discuss the progression of our understanding and evolving thinking around seizure emergencies
- Examine the available treatments for terminating a seizure emergency, taking a close look at mode of administration and pharmacokinetic profiles
- Review the importance of seizure action plans in all phases of life

Categorizing seizure emergencies¹



ARS, Acute repetitive seizures. *Definition of generalized convulsive status epilepticus.

1. Asnis-Alibozek A, et al. *Epilepsy Behav Rep.* 2021;15:100409. 2. Epilepsy Foundation of Minnesota. Accessed February 18, 2025. <https://www.epilepsyfoundationmn.org/2020/01/14/acute-repetitive-seizures-ars-or-cluster-seizures/> 3. Lowenstein DH, et al. *Epilepsia.* 1999;40(1):120-122. 4. Trinka E, et al. *Epilepsia.* 2015;56(10):1515-1523.

Seizure emergencies and epilepsy are associated with increased mortality^{1,2}

2X

Risk of premature mortality for people with epilepsy¹

4X

Risk of dying for patients who progressed to SE in a 30-year study²

15.6%

Mortality in adults with SE from a systematic meta-analysis of 30 studies³

In a cohort of people with epilepsy,

16%

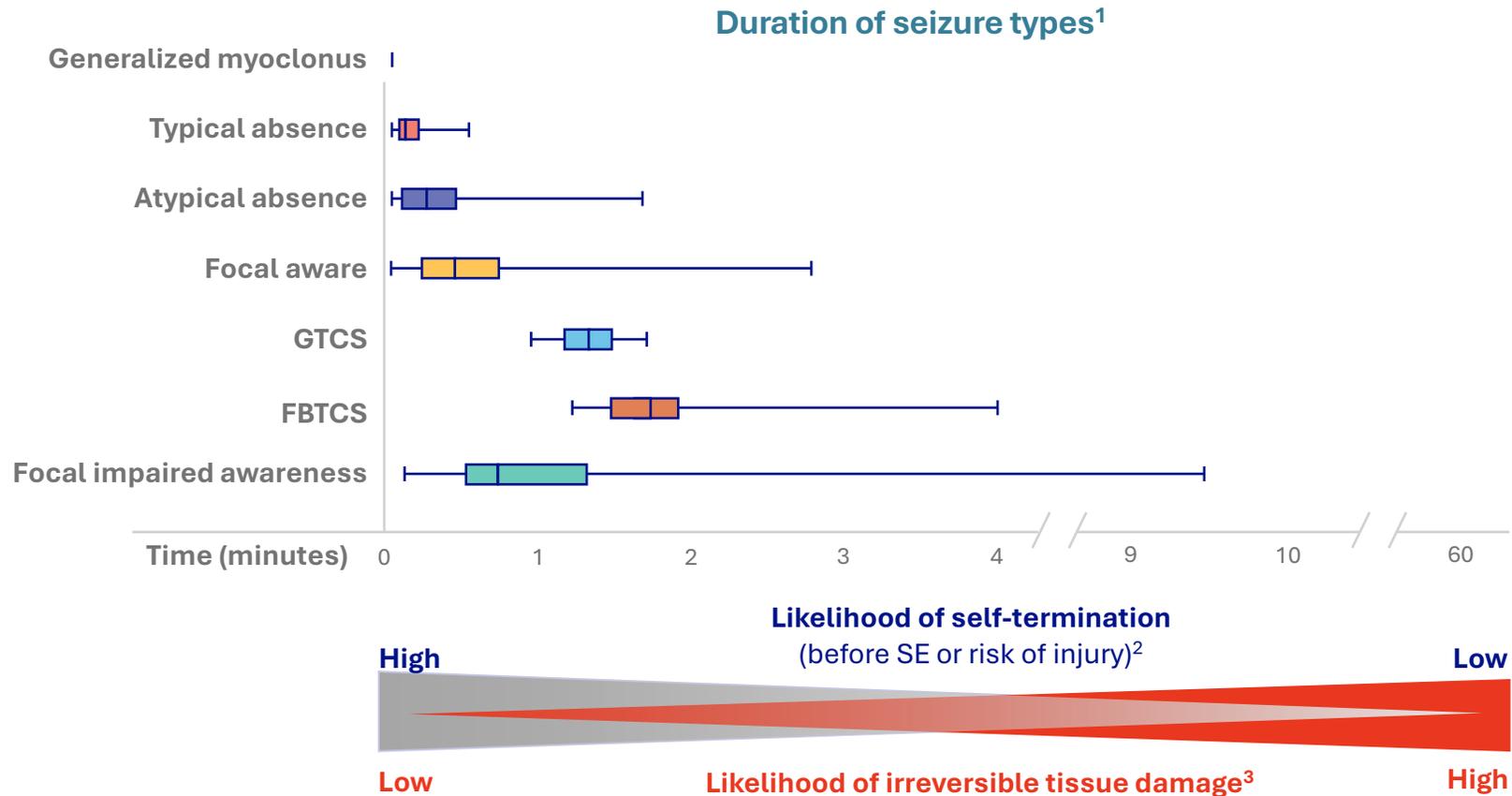
Of people died of SE⁴

Causes of death among people with epilepsy include injuries, SE, and sudden unexpected death in epilepsy (SUDEP), which may be preventable with access to high-quality specialty healthcare¹

SE, status epilepticus

1. Thurman DJ, et al. *Epilepsia*. 2017;58(1):17-26. 2. Logroscino G, et al. *Arch Neurol*. 2008;65(2):221-224. 3. Neligan A, et al. *JAMA Neurol*. 2019;76(8):897-905. 4. Sander JW, et al. *J Neurol Neurosurg Psychiatry*. 2004;75(3):349-351.

How long do seizures typically last?



Most epileptic seizures will terminate within

2 minutes

However, some seizures can become prolonged or progress to a more severe seizure⁴⁻⁶

Figure adapted from Meritam Larsen P, et al. *Epilepsia*. 2023;64(2):469–78.

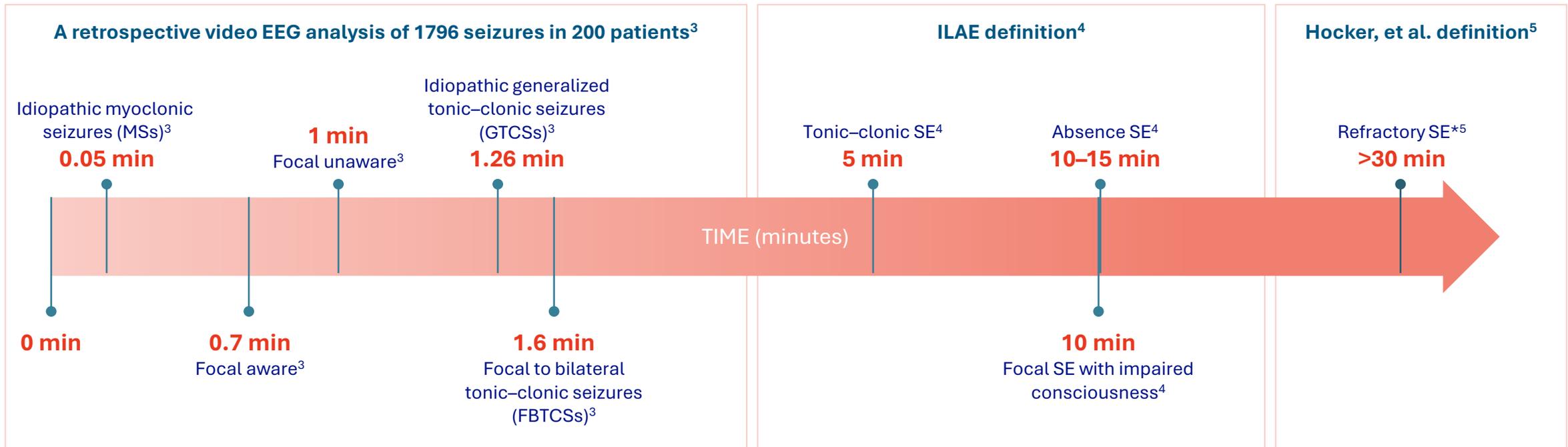
FBTCS, focal to bilateral tonic-clonic seizure; GTCS, generalized tonic-clonic seizure; SE, status epilepticus.

1. Meritam Larsen P, et al. *Epilepsia*. 2023;64(2):469–478. 2. Pellock JM. *J Child Neurol*. 2007;22(Suppl 5):9S–13S. 3. Trinka E, et al. *Epilepsia*. 2015;56(10):1515–1523. 4. Jenssen S, et al. *Epilepsia*. 2006;47(9):1499–1503. 5. Shinnar S. *J Child Neurol*. 2007;22(5 Suppl):14S–20S. 6. Ferastraoaru V, et al. *Epilepsia*. 2016;57(6):889–895.

Relevance of seizure duration and progression

Any seizure carries a risk of progression to a more severe seizure (ie, focal to bilateral tonic-clonic) or a seizure emergency (ie, seizure cluster, prolonged seizure or SE)^{1,2}

Seizures → Prolonged seizures → SE → Refractory SE



Median seizure durations calculated from seconds.

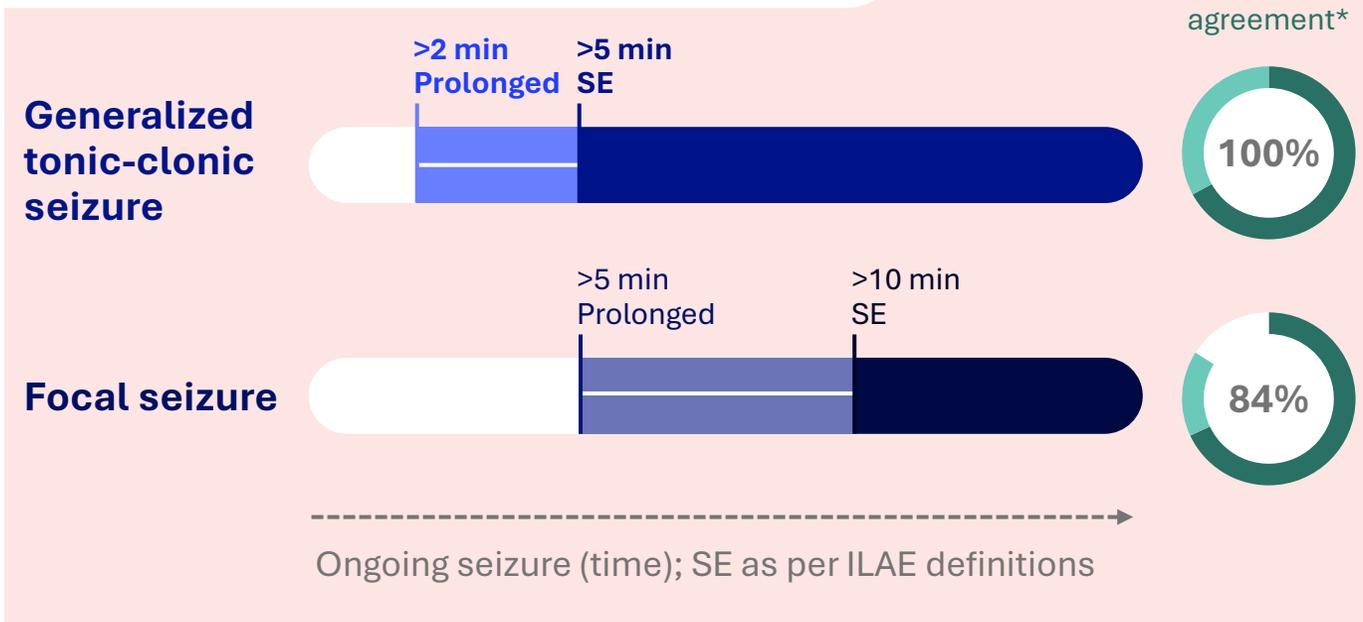
*Refractory SE is defined as ongoing or recurrent seizure activity despite two appropriately selected and dosed anti-epileptic drugs, including a benzodiazepine.

EEG, electroencephalogram; FBTCS, focal to bilateral tonic-clonic seizure; GTCS, generalized tonic-clonic seizure; ILAE, International League Against Epilepsy; MS, myoclonic seizure; SE, status epilepticus.

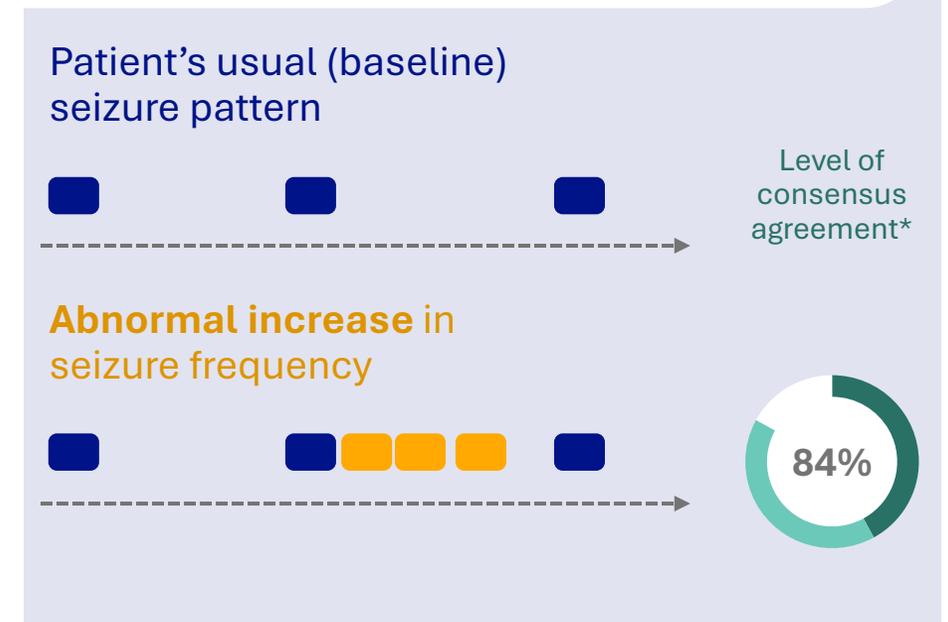
1. Sharma S, Detyniecki K. *Curr Opin Neurol.* 2022;35(2):155-160. 2. Asnis-Alibozek A, et al. *Epilepsy Behav Rep.* 2021;15:100409. 3. Dobeberger J, et al. *Epilepsy Behav.* 2015;49:111-117; 4. Trinka E, et al. *Epilepsia.* 2015;56(10):1515-1523; 5. Hocker S, et al. *Curr Neurol Neurosci Rep.* 2014;14:452.

Evolving definition for prolonged seizures; differentiating from a seizure cluster

? What is the **definition of a prolonged seizure?**



? What is the **definition of a seizure cluster?**



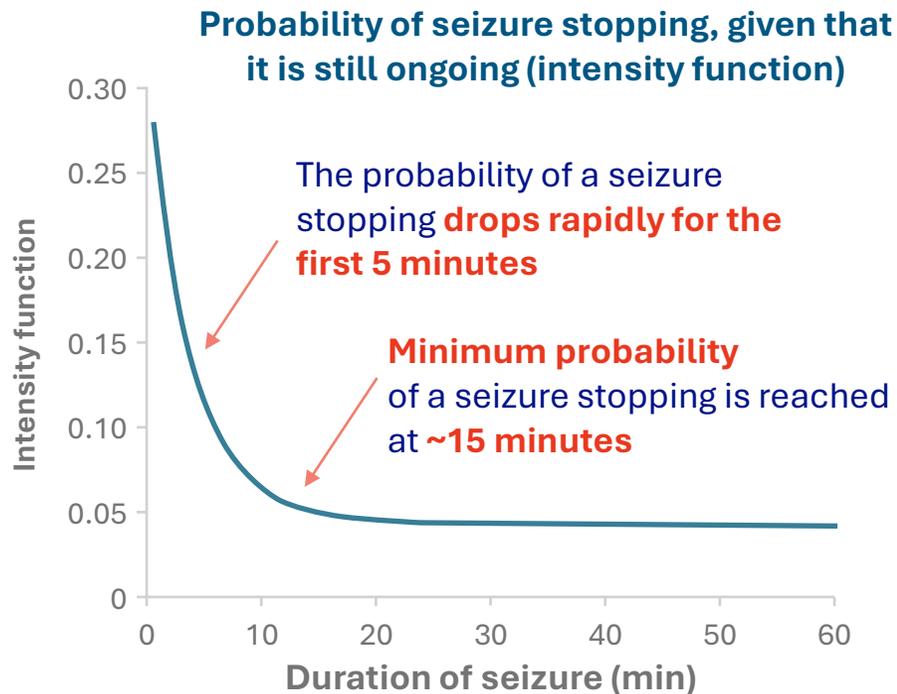
*These are recommendations from an expert working group – comprised of 12 epileptologists, neurologists, and pharmacologists from Europe and North America. A modified Delphi consensus methodology was used to develop and anonymously vote on statements. Consensus was defined as $\geq 75\%$ voting “Agree”/“Strongly Agree.”

ILAE, International League Against Epilepsy; SE, status epilepticus.

Pina-Garza JE, et al. *Epileptic Disord.* 2024;26:484-497.

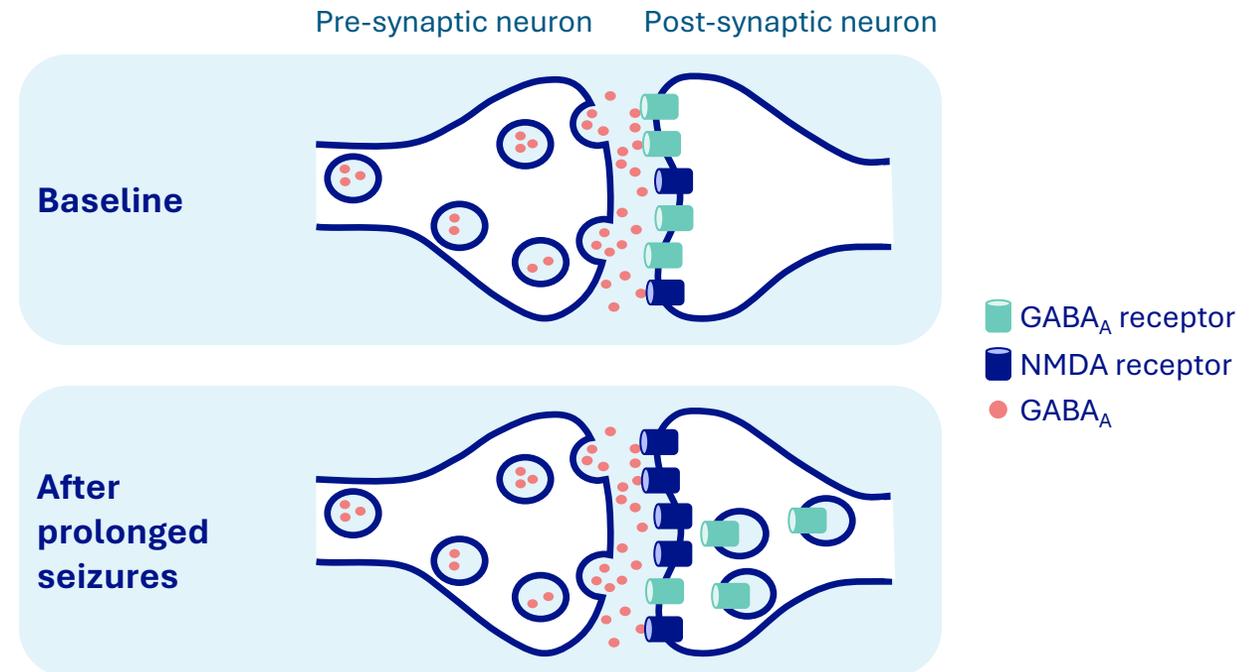
The longer a seizure lasts, the less likely it is to self-terminate or respond to treatment¹⁻⁴

SE becomes more difficult to control as its duration increases^{1,2}



Adapted from Shinnar S. *J Child Neurol.* 2007.

Response to BZDs decreases with increasing seizure duration^{1,4}



Adapted from Becker DA, et al. *Neurol Ther.* 2023.

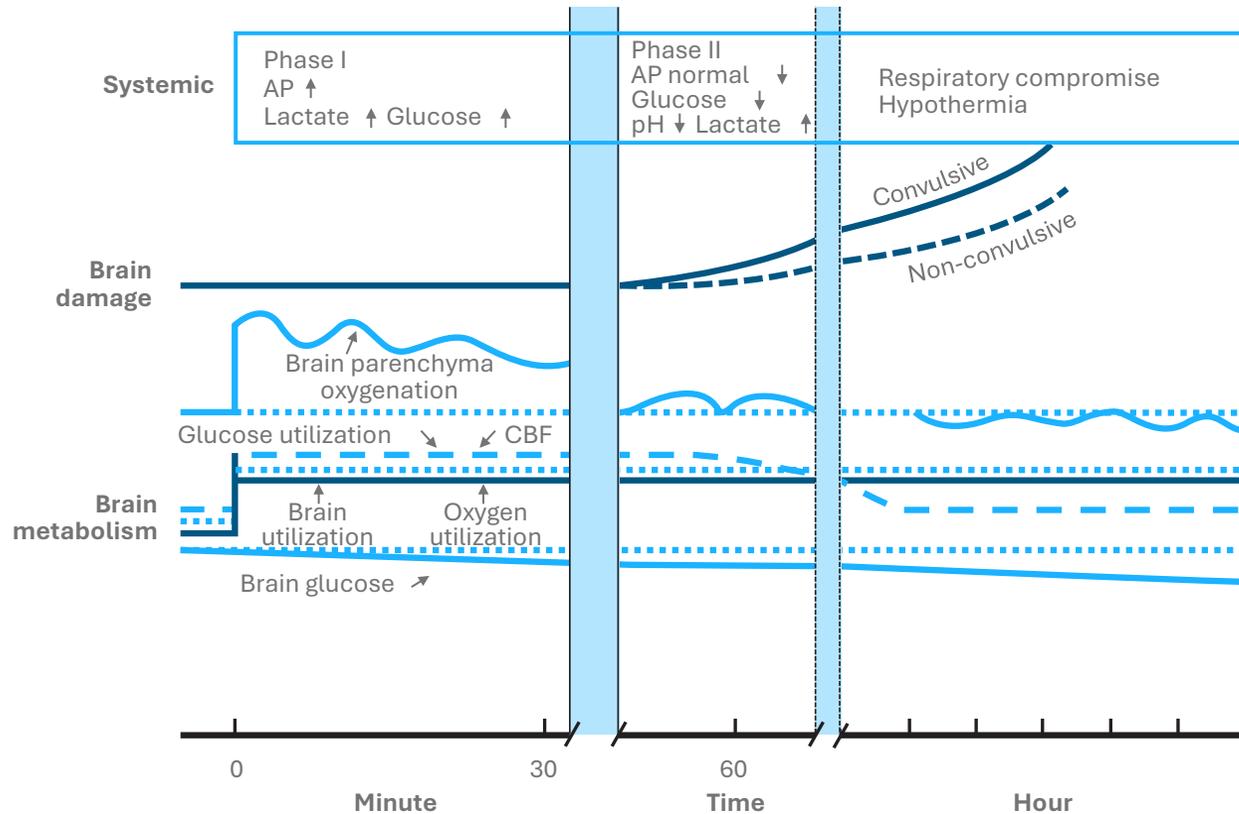
BZD, benzodiazepine; GABA_A, gamma-aminobutyric acid A; NMDA, N-methyl-D-aspartate; SE, status epilepticus.

1. Naylor DE. *Epileptic Disord.* 2014;16(Suppl 1):S69-S83. 2. Pellock JM. *J Child Neurol.* 2007;22(Suppl 5):9S-13S. 3. Shinnar S. *J Child Neurol.* 2007;22(5 Suppl):14S-20S.

4. Becker DA, et al. *Neurol Ther.* 2023;12(5):1439-1455.

What are the risks of seizures that progress?

Physiological changes occurring during prolonged status epilepticus¹



Physical injury²



Brain injury and neuronal death²⁻⁴



Increased healthcare resource utilization and costs^{*5-7}



Reduced QoL and impacted societal outcomes^{5,8}

Adapted from Perks A, et al. *Br J Anaesth*. 2012.

*Including hospitalization costs associated with status epilepticus, and indirect costs such as loss of income for caregivers.^{5,6}

AP, alkaline phosphatase; CBF, cerebral blood flow; QoL, quality of life.

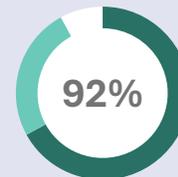
1. Perks A, et al. *Br J Anaesth*. 2012;108(4):562-571.
2. Asnis-Alibozek A, et al. *Epilepsy Behav Rep*. 2021;15:100409.
3. Naylor DE. *Epileptic Disord*. 2014;16(Spec No 1):S69-S83.
4. Betjemann JP, Lowenstein DH. *Lancet Neurol*. 2015;14(6):615-624.
5. Kortland LM, et al. *Front Neurol*. 2017;8:507.
6. Sculier C, et al. *Epilepsia*. 2018;59(Suppl 2):155-169.
7. Lee DC, et al. *Health Econ Rev*. 2014;4:6.
8. Shinnar S. *J Child Neurol*. 2007;22(5 Suppl):14S-20S.

Current treatment paradigm: Acute Cluster Treatment (ACT)

? What is ACT?

Acute cluster treatment (ACT) is a medication with the ability to prevent the next or **further seizures** in a **cluster of seizures**

Level of consensus agreement*



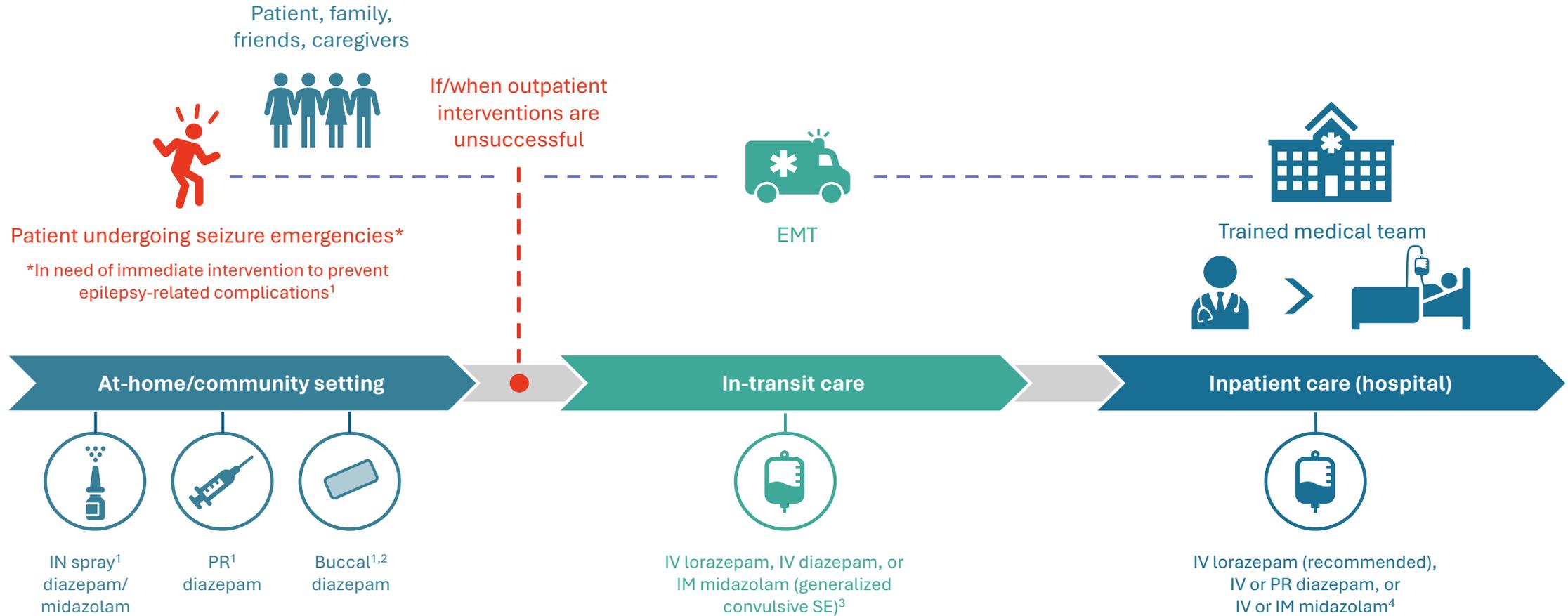
Patient's usual (baseline) seizure pattern



Abnormal increase in seizure frequency



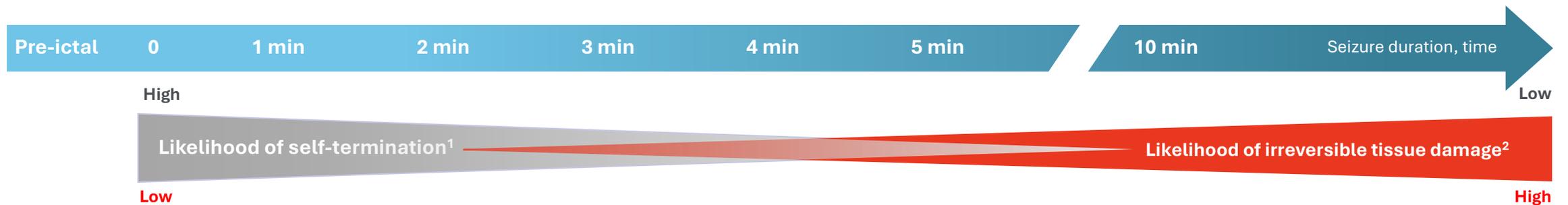
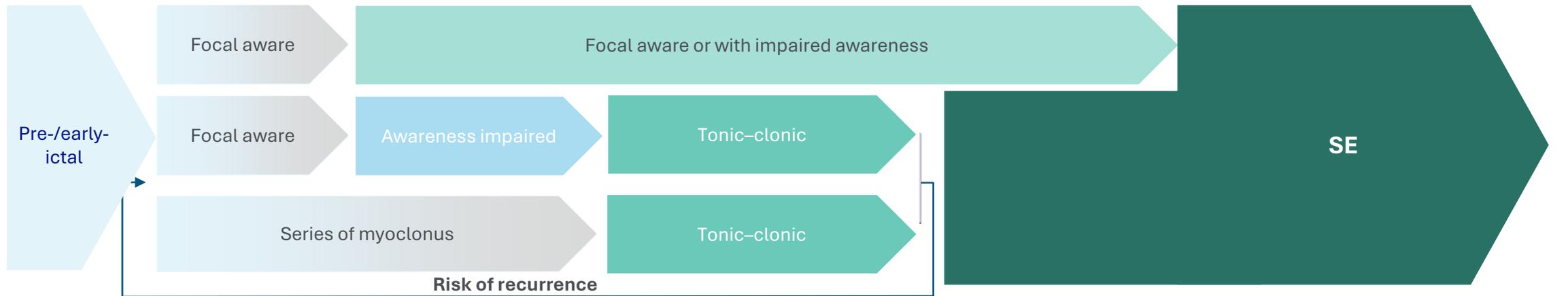
The current seizure emergency treatment journey



EMT, emergency medical technician; IN, intranasal; PR, per rectum; IM, intramuscular; IV, intravenous; SE, status epilepticus.

1. Asnis-Alibozek A, et al. *Epilepsy Behav Rep.* 2021;15:100409. 2. LIBERVANT® (diazepam) buccal film PI. <https://aquestive.com/content/uploads/libervant-2-to-5-years-of-age-pi-clean-pdf.pdf> Accessed March 28, 2025. 3. Betjemann JP, et al. *JAMA.* 2019;321(12):1216-1217. 4. emDocs. Treatment of seizures in the emergency department: pearls and pitfalls; Dec 2015. Accessed March 11, 2025. <https://www.emdocs.net/treatment-of-seizures-in-the-emergency-department-pearls-and-pitfalls/>

What is the window of opportunity to stop seizures before progression?

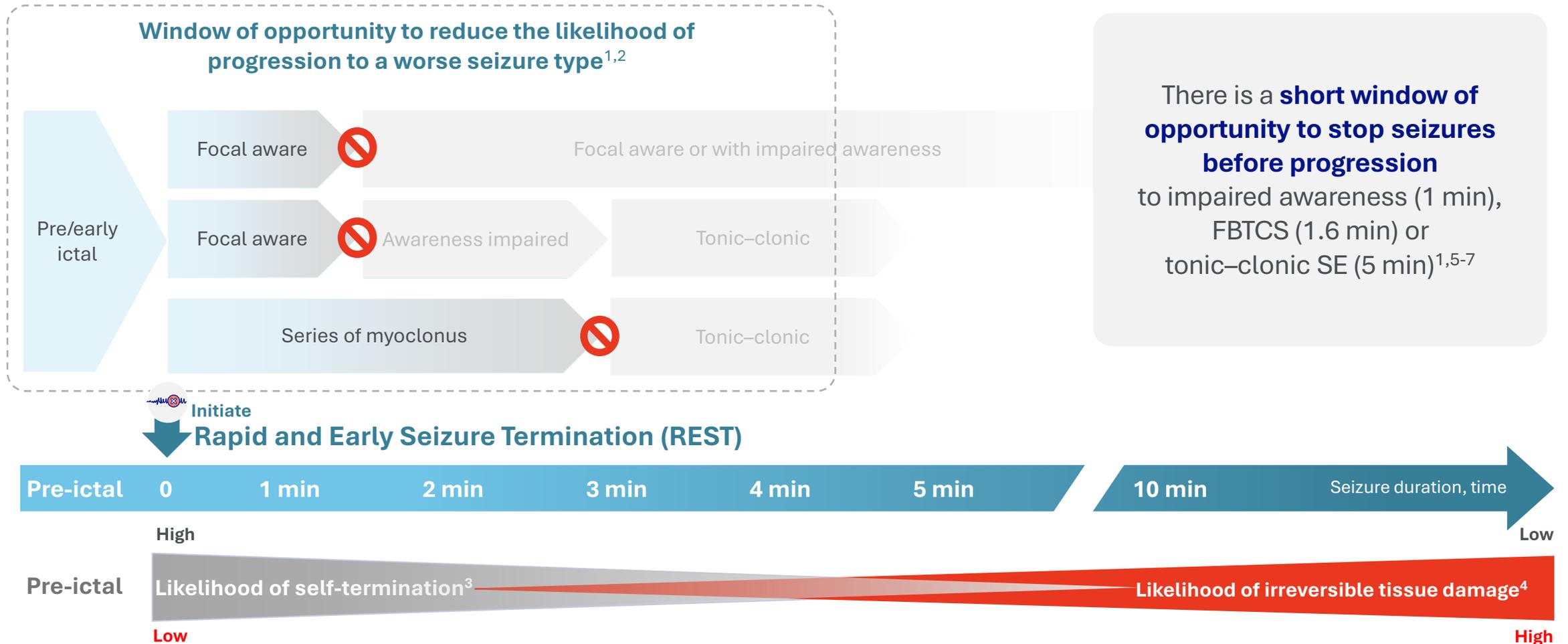


This timeline does not contain precise timings.

SE, status epilepticus.

1. Pellock JM. *J Child Neurol.* 2007;22(5 Suppl):9S-13S. 2. Trinka E, et al. *Epilepsia.* 2015;56(10):1515-1523.

What is the window of opportunity to stop seizures before progression? (2/2)



This timeline does not contain precise timings.

FBTCS, focal to bilateral tonic-clonic seizure; SE, status epilepticus.

1. Meritam Larsen P, et al. *Epilepsia*. 2023;64(2):469-478. 2. Asnis-Alibozek A, et al. *Epilepsy Behav Rep*. 2021;15:100409. 3. Pellock JM. *J Child Neurol*. 2007;22(Suppl 5):9S-13S. 4. Trinka E, et al. *Epilepsia*. 2015;56(10):1515-1523. 5. Sharma S, Detyniecki K. *Curr Opin Neurol*. 2022;35(2):155-160. 6. Blond BN, Hirsch LJ. *Expert Rev Neurother*. 2022;22(7):567-577. 7. Dobesberger J, et al. *Epilepsy Behav*. 2015;49:111-117.

The evolving treatment paradigm: Rapid and Early Seizure Termination (REST)

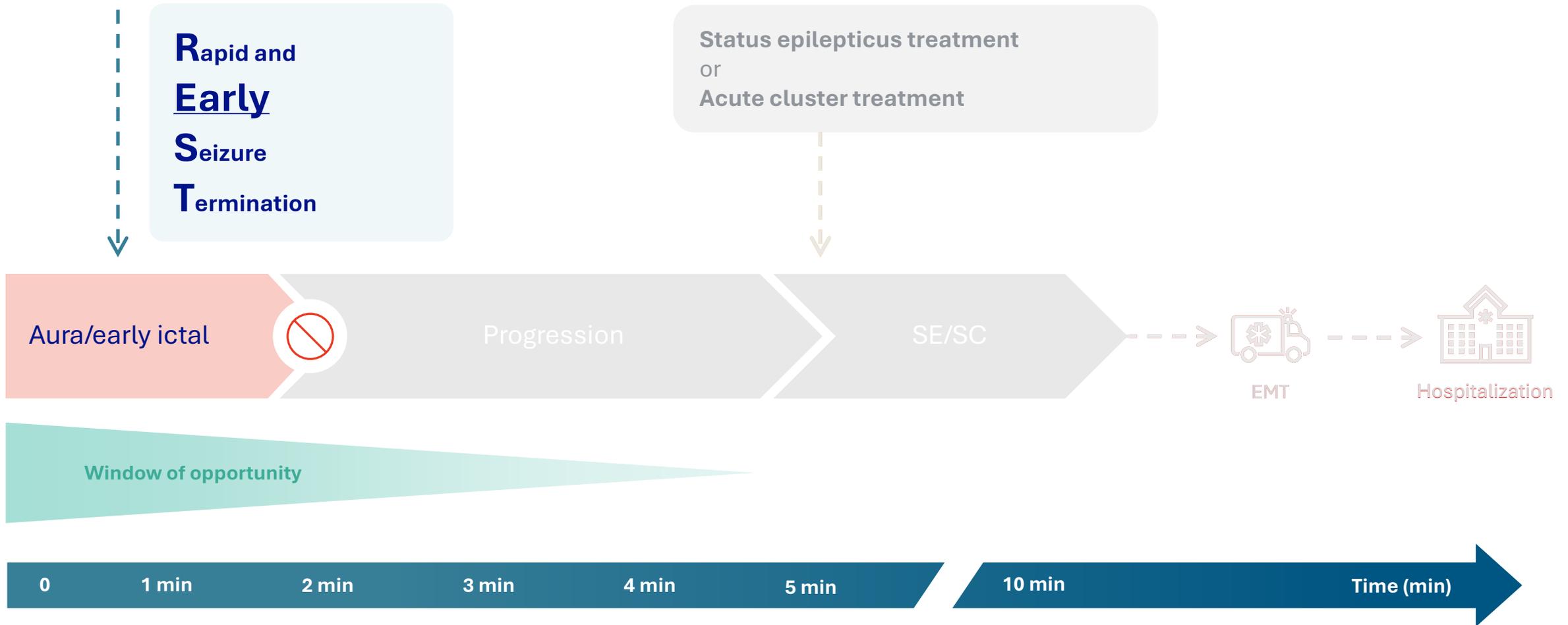


Early administration with a **rapidly acting** treatment, with the goal of seizure termination in as short a time as possible and **preventing progression** to a more severe seizure



An **ideal Rapid and Early Seizure Termination (REST) medication** would start to **act within 2 minutes of administration** to terminate an ongoing seizure

Seizure emergencies: prevention instead of “rescue”?



When to administer treatment? REST vs ACT

? When should REST be administered?



As **EARLY** as possible when onset recognizable

Prolonged seizure

92%

Seizure onset

? When should ACT be administered?



When cluster onset recognized based on **abnormal seizure pattern**

100%

Individual seizure episodes (time)

92% and 100% refer to the level of consensus agreement.
ACT, acute cluster treatment; REST, Rapid and Early Seizure Termination.
Pina-Garza JE, et al. *Epileptic Disord.* 2024;26(4):487-497.

Current routes of administration for acute neurologic conditions

Acute Neurologic Condition	Medication	Administration Route
Migraine ¹	Dihydroergotamine	IM, IV, and SC injection, intranasal
Off episodes in Parkinson's disease ²	Levodopa inhalation powder	Oral inhalation
Flares in multiple sclerosis or systemic lupus erythematosus ³	Repository corticotropin injection	IM and SC injection
Seizures, seizure clusters, and status epilepticus^{4,5}	Benzodiazepines	IM and IV injection, oral, buccal, rectal, intranasal

This table is not an exhaustive list.

IM, intramuscular; IV, intravenous; SC, subcutaneous.

1. Silberstein SD, et al. *Headache*. 2020;60:40-57. 2. Inbrija (levodopa inhalation powder) PI. <https://www.inbrija-hcp.com>. Accessed March 6, 2025. 3. Acthar gel (repository corticotropin injection) PI. <https://www.acthar.com>. Accessed March 6, 2025. 4. Kienitz R, et al. *CNS Drugs*. 2022;36(9):951-975. 5. LIBERVANT® (diazepam) buccal film PI. <https://aquestive.com/content/uploads/libervant-2-to-5-years-of-age-pi-clean-pdf.pdf> Accessed March 28, 2025.

What are the unmet needs in current routes of administration for on-demand ASMs?

Mapping today's on-demand medications against the characteristics of an ideal Rapid and Early Seizure Termination (REST) medication, we see that there are gaps

Molecule/Route of Administration	Ideal characteristics common to all on-demand medications			Ideal REST characteristics	
	Effective against a range of seizure types	Non-invasive RoA	Outpatient administration	Rapid seizure cessation	Self-administration
Oral ¹⁻³	Green	Green	Green	Red	Green
Intramuscular ^{1,2,4,5}	Green	Yellow	Red	Yellow	Red
Rectal ^{1,2,6}	Green	Yellow	Yellow	Red	Red
Nasal ^{1,2,7,8}	Green	Green	Green	Yellow	Green
Oromucosal/sublingual ^{1,2,9,10}	Green	Green	Green	Red	Green
Intravenous ¹	Green	Red	Red	Green	Red

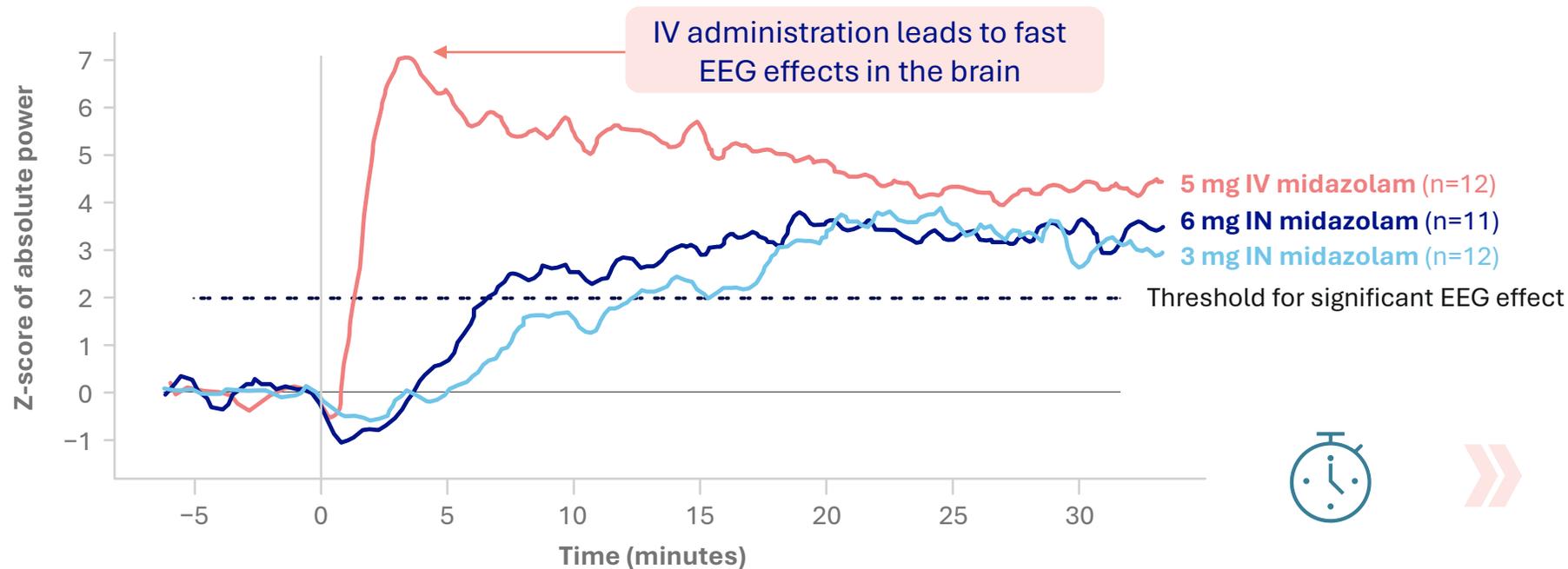
Green = achieves the desired characteristic, Yellow = sometimes achieves the desired characteristic, Red = does not achieve the desired characteristic.

The material presented may contain unapproved indications and/or use and/or products. Licenses may vary by country. Please always refer to the prescribing information in your country before prescribing any drug. ASM, anti-seizure medication; RoA, route of administration.

1. Kienitz R, et al. *CNS Drugs*. 2022;36:951-957. 2. Almohaish S, et al. *J Clin Med*. 2021;10:1754. 3. KLOPIN® (Clonazepam) tablet PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/017533s062lbl.pdf. Accessed March 3, 2025. 4. CEREBYX® (fosphenytoin sodium) injection for intravenous or intramuscular use PI. <https://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=749> Accessed February 24, 2025. 5. Midazolam injection for intramuscular use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/216359s000lbl.pdf Accessed February 24, 2025. 6. DIASTAT® (diazepam) rectal gel PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020648s023lbl.pdf Accessed February 24, 2025. 7. VALTOCO® (diazepam) nasal spray PI. https://valtoco.com/VALTOCO_Prescribing_Information.pdf. Accessed February 24, 2025. 8. NAYZILAM® (midazolam) nasal spray PI. <https://www.ucb-usa.com/nayzilam-prescribing-information.pdf>. Accessed February 24, 2025. 9. SYMPAZAN® (clobazam) oral film PI. <https://www.sympazan.com/pdfs/pi.pdf> Accessed February 24, 2025. 10. LIBERVANT® (diazepam) buccal film PI. <https://aquestive.com/content/uploads/libervant-2-to-5-years-of-age-pi-clean-pdf.pdf> Accessed March 28, 2025.

The route of administration influences the time to EEG effects in the brain

EEG effect curves of IV or IN midazolam*†



Median time to EEG effects in the brain:‡

- 5 mg IV: **1.2 minutes**
- 6 mg IN: **5.5 minutes**
- 3 mg IN: **6.9 minutes**

Adapted from Hardmeier M, et al. Clin Pharmacol Ther. 2012.

NOTE: The intranasal midazolam used in this study is not the same product as Nayzilam (midazolam) nasal spray.

*Mean time course of absolute power in the combined spindle and β_1 frequency bands (12–18 Hz) expressed as Z-scores (moving average over 1 minute) after treatment administration. SDs are omitted for clarity. †The dotted horizontal line marks the threshold for significant EEG effects (>2 SD relative to baseline power for >60 s). ‡Using times to onset of significant EEG effects in the β_2 band (18–25 Hz) as a central pharmacodynamic marker as a proxy for time to onset of action.

β_1 , beta 1; β_2 , beta 2; EEG, electroencephalogram; Hz, hertz; IN, intranasal; IV, intravenous; SD, standard deviation.

Hardmeier M, et al. Clin Pharmacol Ther. 2012;91(5):856-862.

Building seizure duration into the seizure action plan discussion

Understanding of specific seizure emergencies may allow an individualized approach to the recommendation for rescue treatment according to patient presentation and type of seizure emergency¹

Seizure action plan (SAP)²

SEIZURE ACTION PLAN (SAP)  **END EPILEPSY**

Name: _____ Birth Date: _____
 Address: _____ Phone: _____
 Emergency Contact/Relationship: _____ Phone: _____

Seizure Information

Seizure Type	How Long It Lasts	How Often	What Happens

How to respond to a seizure (check all that apply)

First aid - Stay, Safe, Side. Notify emergency contact at _____
 Give rescue therapy according to SAP Call 911 for transport to _____
 Notify emergency contact Other _____

First aid for any seizure

STAY calm, keep calm, begin timing seizure
 Keep me SAFE - remove harmful objects, don't restrain, protect head
 SIDE - turn on side if not awake, keep airway clear, don't put objects in mouth
 STAY until recovered from seizure
 Sleepy suggest for VNS
 Write down what happens _____
 Other _____

When to call 911

Seizure with loss of consciousness longer than 5 minutes, not responding to rescue med if available
 Repeated seizures longer than 10 minutes, no recovery between doses, not responding to rescue med if available
 Difficulty breathing after seizure
 Seizures injury occurs or suspected, seizure in water

When to call your provider first

Change in seizure type, number or pattern
 Person does not return to usual behavior (e.g., confused for a long period)
 First time seizure that steps on his own
 Other medical problems or pregnancy need to be checked

When rescue therapy may be needed:

WHEN AND WHAT TO DO

If seizure (cluster, # or length) _____
 Name of Med/Rx: _____ How much to give (dose) _____
 How to give _____

If seizure (cluster, # or length) _____
 Name of Med/Rx: _____ How much to give (dose) _____
 How to give _____

If seizure (cluster, # or length) _____
 Name of Med/Rx: _____ How much to give (dose) _____
 How to give _____

Seizure Action Plan continued

Care after seizure
 What type of help is needed? (describe) _____
 When is person able to resume usual activity? _____

Special instructions
 First Responders: _____
 Emergency Department: _____

Daily seizure medicine

Medicine Name	Total Daily Amount	Amount of Tab/Liquid	How Taken (time of each dose and how much)

Other information
 Trigger: _____
 Important Medical History: _____
 Allergies: _____
 Epilepsy Surgery (type, date, side effects): _____
 Device: VNS RNS DBS (date implanted) _____
 Diet Therapy Ketogenic Low Glycemic Modified Atkins Other (describe) _____
 Special Instructions: _____

Health care contacts
 Epilepsy Provider: _____ Phone: _____
 Primary Care: _____ Phone: _____
 Preferred Hospital: _____ Phone: _____
 Pharmacy: _____ Phone: _____
 My signature _____ Date _____
 Provider signature _____ Date _____

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 **END EPILEPSY**

Acute seizure action plan (ASAP)³

Acute Seizure Action Plan

Name: _____ Birth date: _____ Today's date: _____
 Care partner phone numbers: _____ Provider name/facility: _____
 _____ Provider phone numbers: _____

Usual Seizure Pattern
 Triggers: _____
 Pattern of seizures: _____
 Allergies: _____
 What the seizures normally look like (Check all that apply) Describe: _____
 Atonic seizure (also called drop) Absence seizure (also called petit mal) Tonic seizure Clonic seizure Focal (impaired awareness seizure (also called complex partial))

Care
Standard Care Needed
 If this happens, _____ provide standard care

 Time the seizure	 Keep person safe	 Don't restrict	 Stay with person	 Keep a record
--	--	--	--	---

Provide Rescue Treatment
 If this happens, _____ provide standard care (above) and rescue treatment

<input type="checkbox"/> Rectum	<input type="checkbox"/> Nose	<input type="checkbox"/> Mouth	<input type="checkbox"/> Other: _____
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Specific instructions: _____

Call for Emergency Help
 If any of these happens, _____
 Seizure longer than _____ minutes Unusual seizure Injury/Bleed lips Other: _____
 Get help now: Call Healthcare Provider if _____
 Call for Emergency Help if _____

Healthcare Provider Authorization
 Signature: _____ Provider Printed Name: _____ Date: _____ For use from: _____ to: _____

1. Asnis-Alibozek A, et al. *Epilepsy Behav Rep.* 2021;15:100409. 2. Epilepsy Foundation. Seizure Action Plan. Accessed March 7, 2025. <https://www.epilepsy.com/sites/default/files/2023-08/SeizureActionPlan2023ACCE.pdf>. 3. Penovich P, et al. *Epilepsy Behav.* 2021;123:108264.

Outpatient REST

Important features of an outpatient **REST** medication



Rapid onset of effect



Ability to terminate an ongoing seizure



Ease of administration by the patient or caregiver



Inspired by **patients.**
Driven by **science.**

Questions?