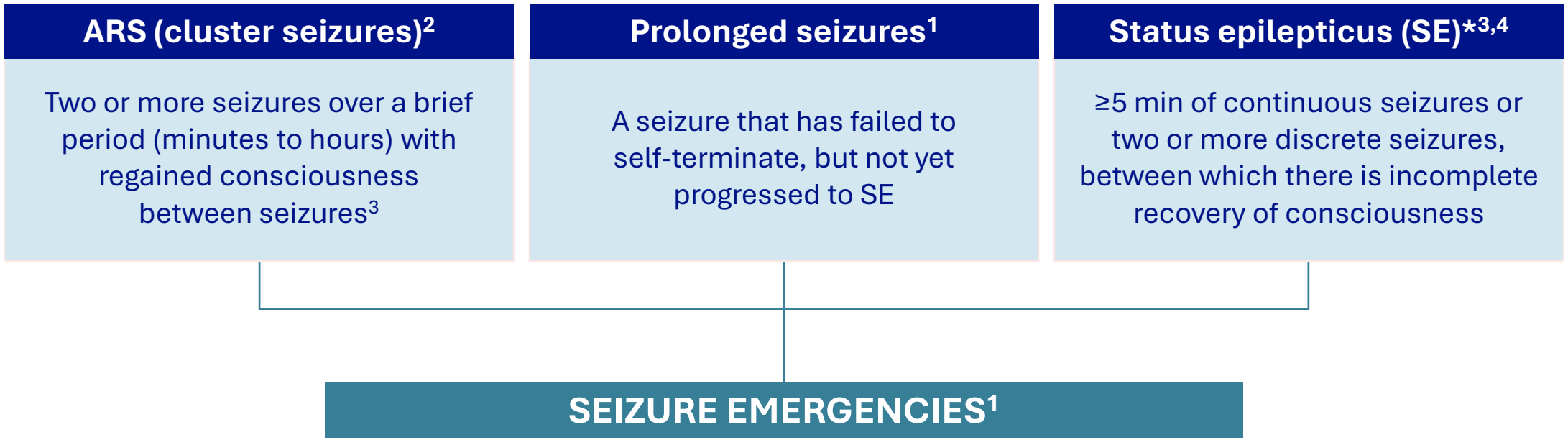
Rethinking Seizure Emergencies

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 emergencies[1]



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 epilepsy[1]

4X

Risk of dying for patients who progressed to SE in a 30-year study[2]

15.6%

Mortality in adults with SE from a systematic meta-analysis of 30 studies[3]

In a cohort of people with epilepsy,

16%

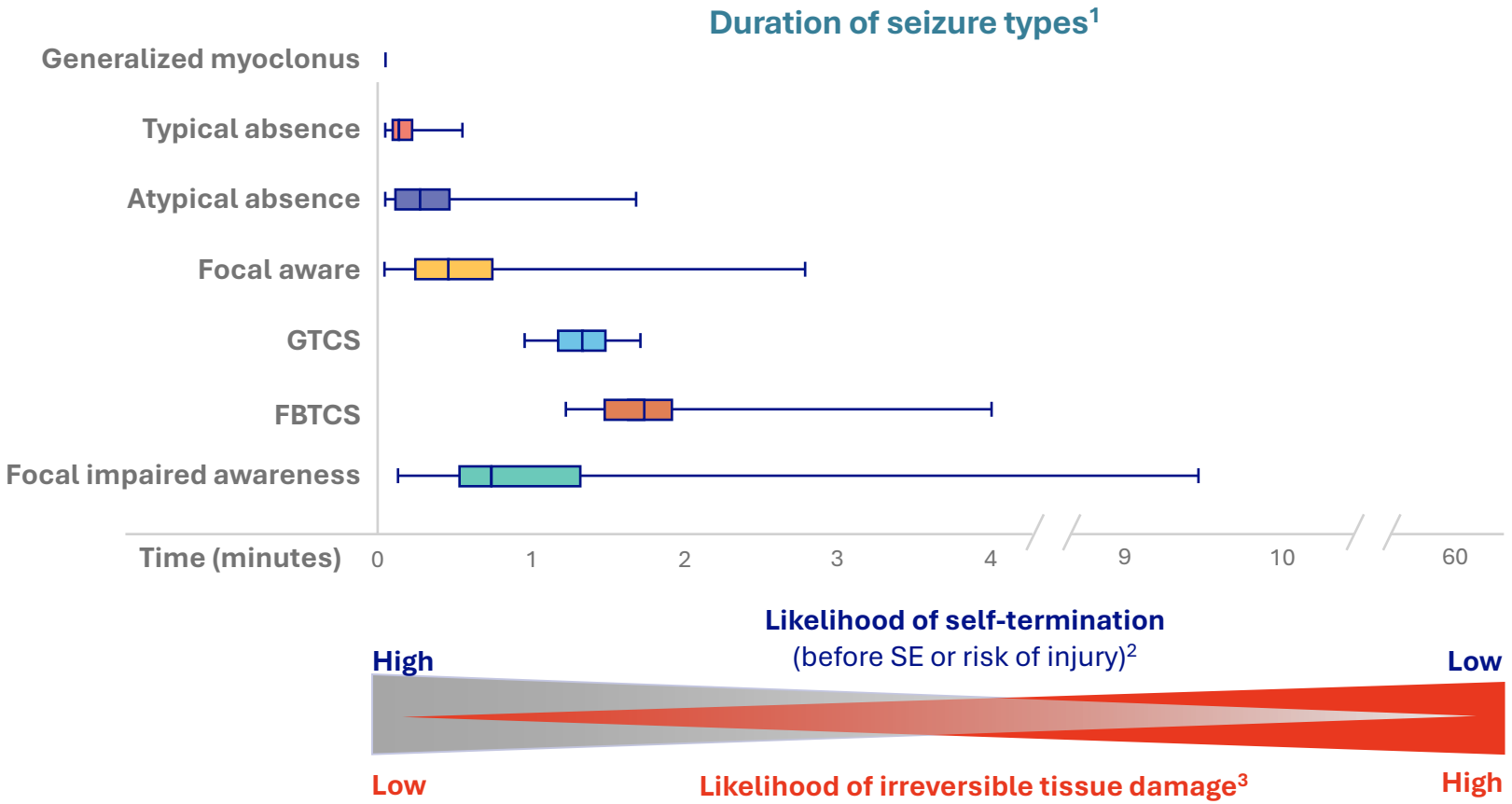
Of people died of SE[4]

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 healthcare[1]

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 seizure[4–6]

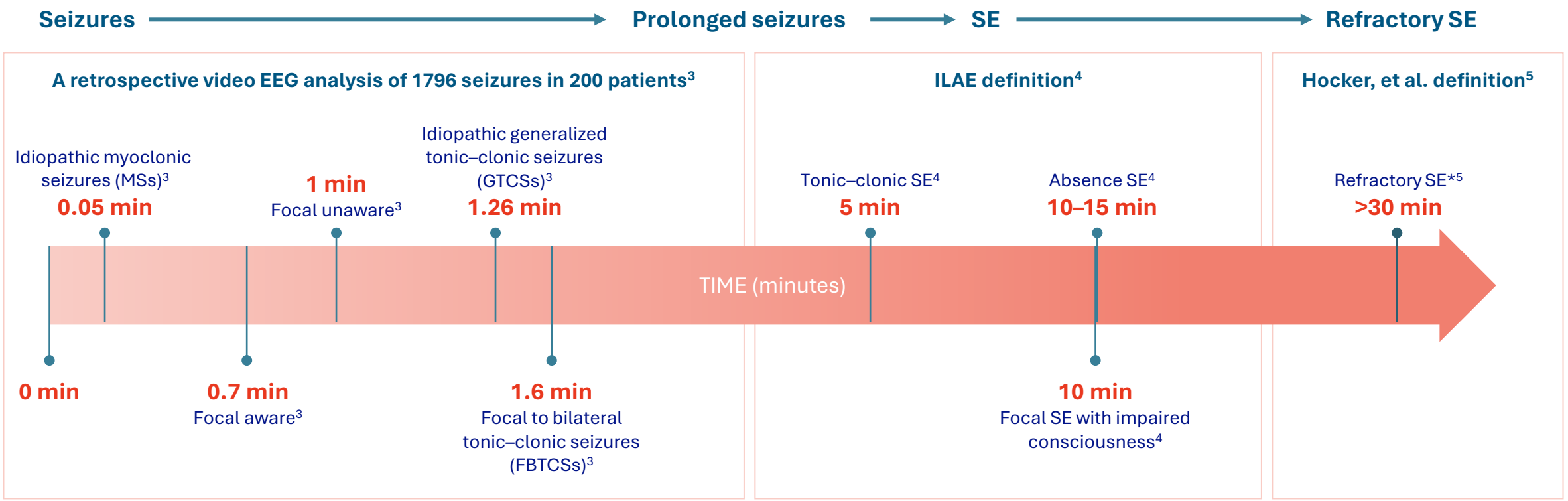
Figure adapted from Meritam Larsen P, et al. Epilepsia. 2023;64(2):469–78.

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]



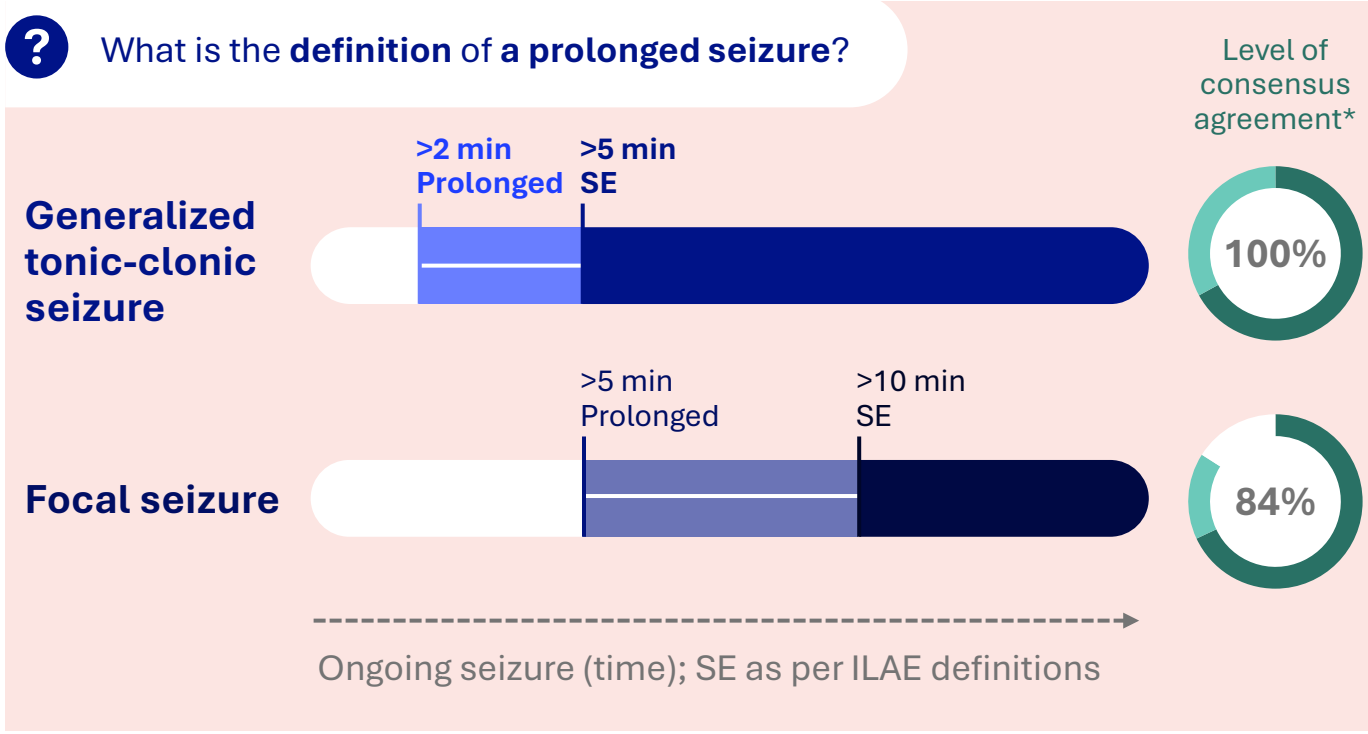
Median seizure durations calculated from seconds.
*Refractory SE is defined as ongoing or recurrent seizure activity despite two appropriately selected and dosed anti-epileptic drugs, including a benzodiazepine.

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.

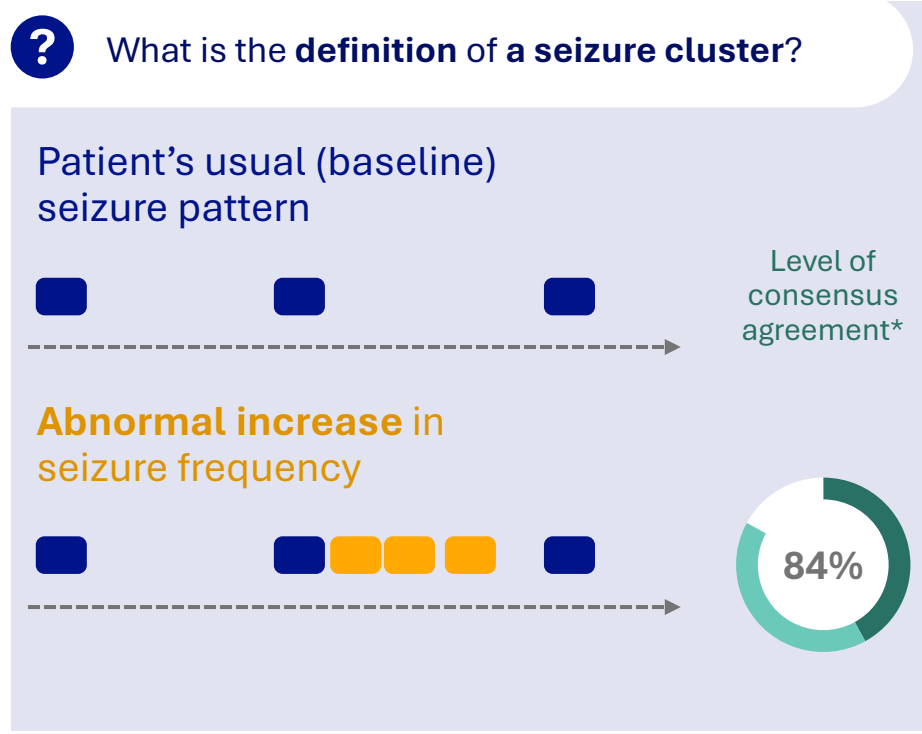
1. Sharma S, Detyniecki K. *Curr Opin Neurol*. 2022;35(2):155-160. 2. Asnis-Alibozek A, et al. *Epilepsy Behav Rep*. 2021;15:100409. 3. Dobesberger J, et al. *Epilepsy Behav*. 2015;49:111-117; 4. Trinka E, et al. *Epilepsia*. 2015;56(10):1515-1523; 5. Hocker S, et al. *Curr Neurol Neurosci Rep*. 2014;14:452.

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**?



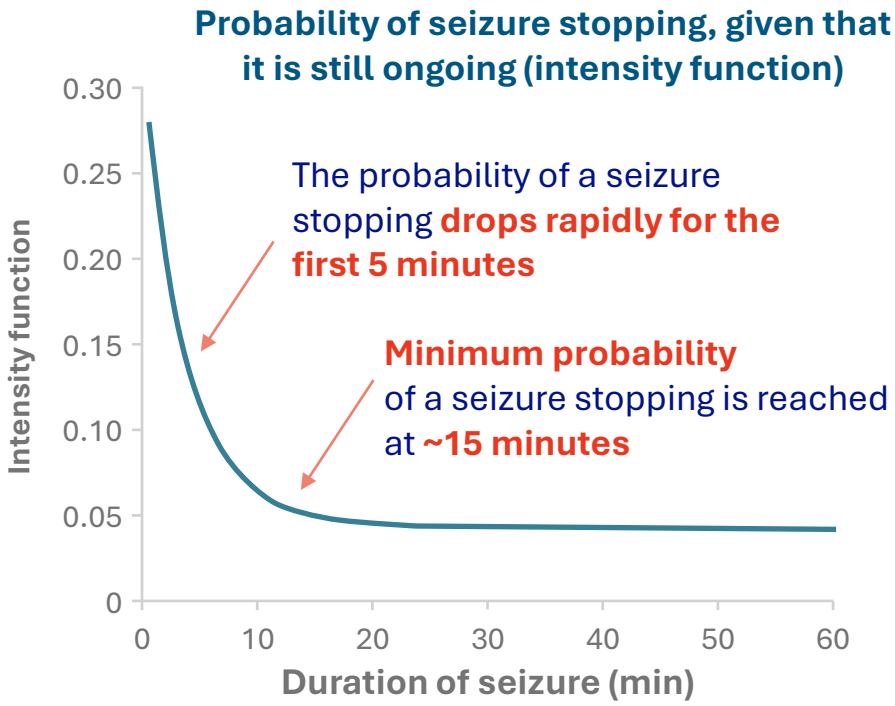
*These are recommendations from an expert working group – comprised of 12 epileptologists, neurologists, and pharmacologists from Europe and North America. A modified Delphi consensus methodology was used to develop and anonymously vote on statements. Consensus was defined as ≥75% voting "Agree"/"Strongly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

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

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

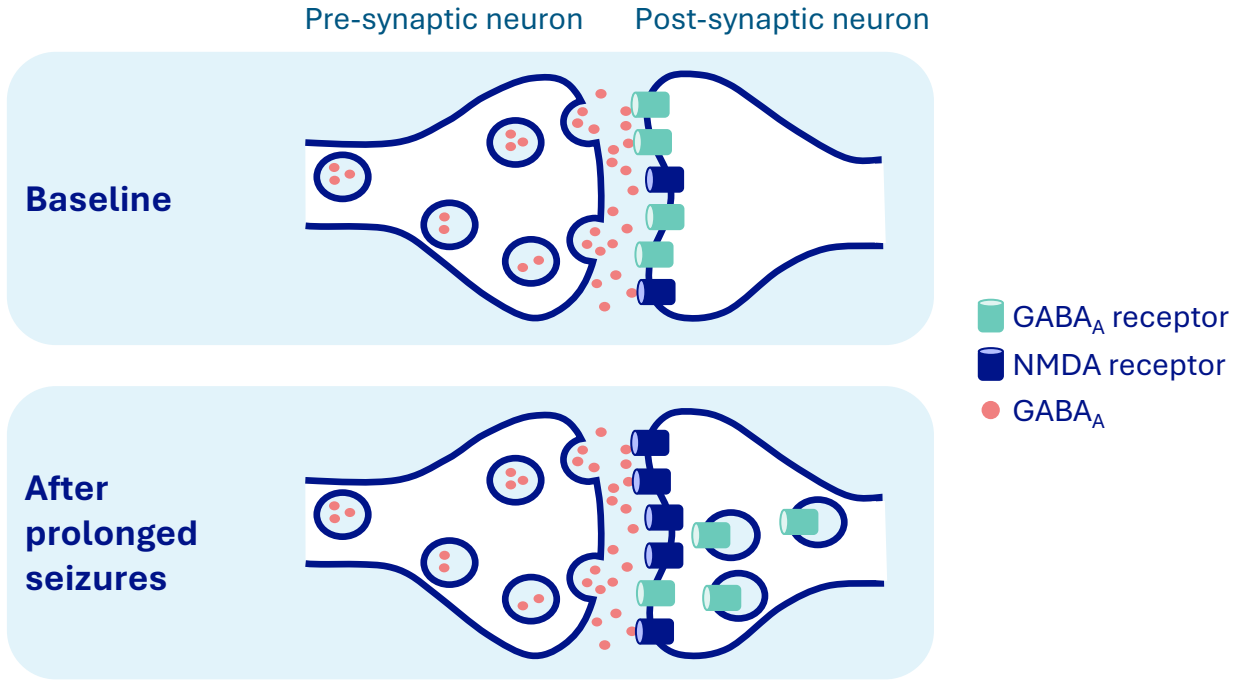
The longer a seizure lasts, the less likely it is to self-terminate or respond to treatment[1–4]

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]



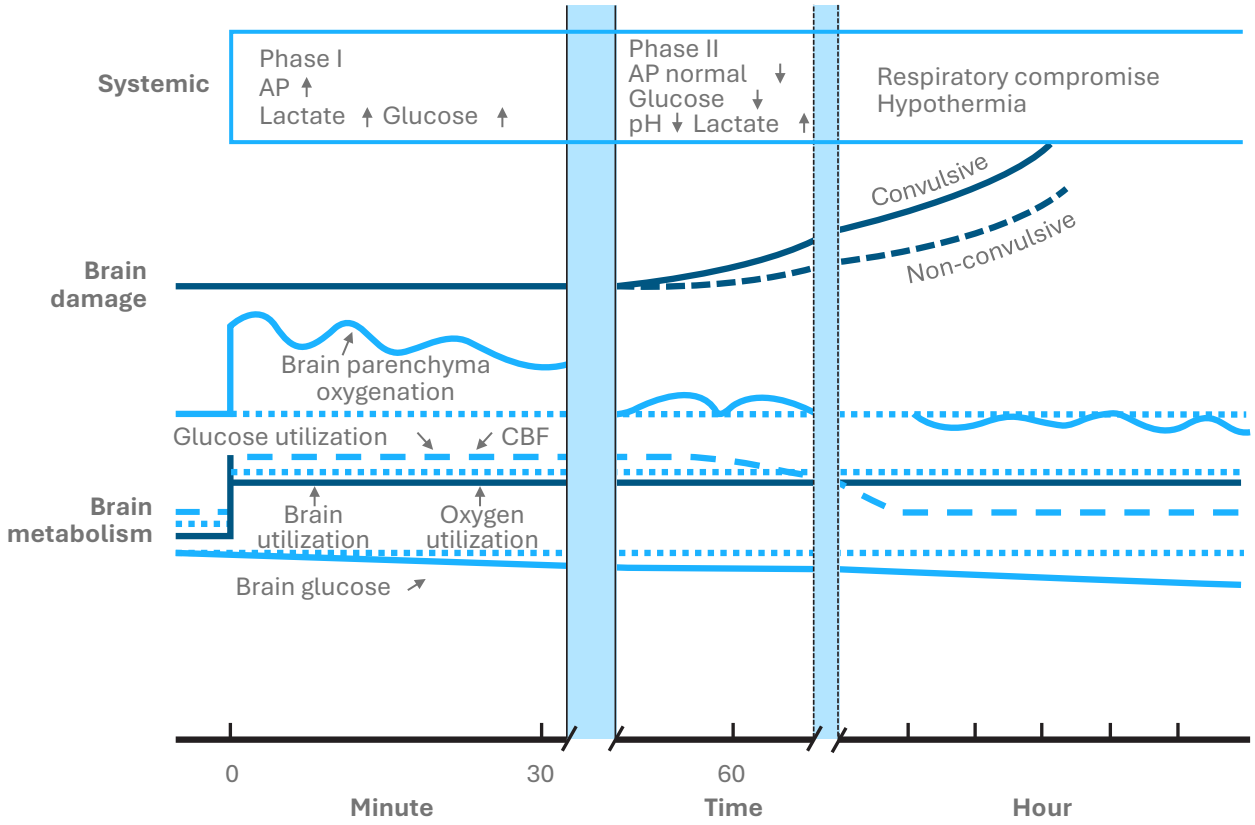
Adapted from Becker DA, et al. *Neurol Ther*. 2023.

BZD, benzodiazepine; GABAA, 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 epilepticus[1]



- Physical injury[2]
- Brain injury and neuronal death[2-4]
- 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.

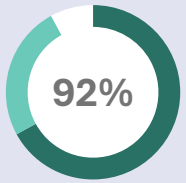
1. Perks A, et al. *Br J Anaesth*. 2012;108(4):562-571. 2. Asnis-Alibozek A, et al. *Epilepsy Behav Rep*. 2021;15:100409. 3. Naylor DE. *Epileptic Disord*. 2014;16(Spec No 1):S69–S83. 4. Betjemann JP, Lowenstein DH. *Lancet Neurol*. 2015;14(6):615-624. 5. Kortland LM, et al. *Front Neurol*. 2017;8:507. 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.

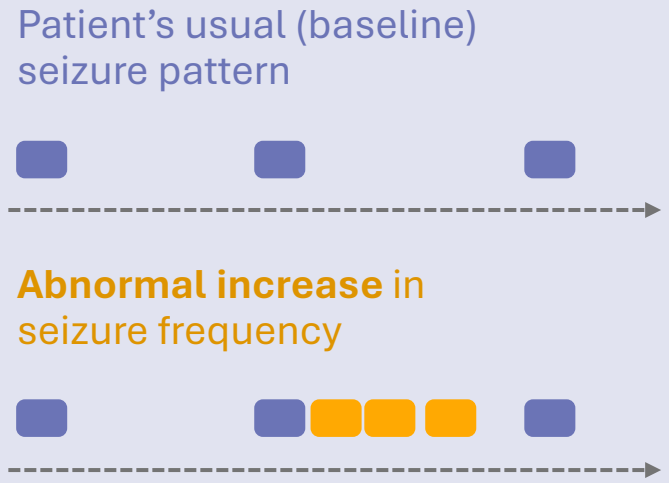
Current treatment paradigm: Acute Cluster Treatment (ACT)

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**

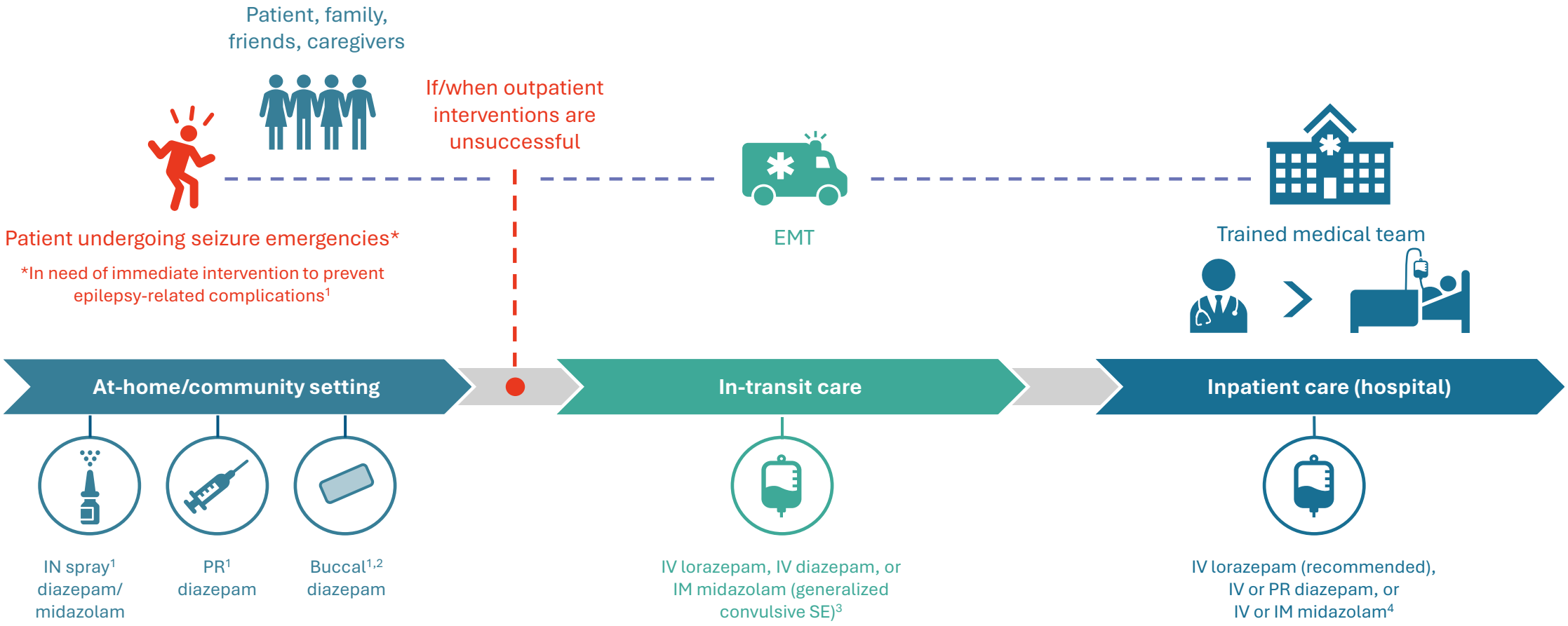
Level of consensus agreement*





Pina-Garza JE, et al. *Epileptic Disord*. 2024;26(4):487-497.

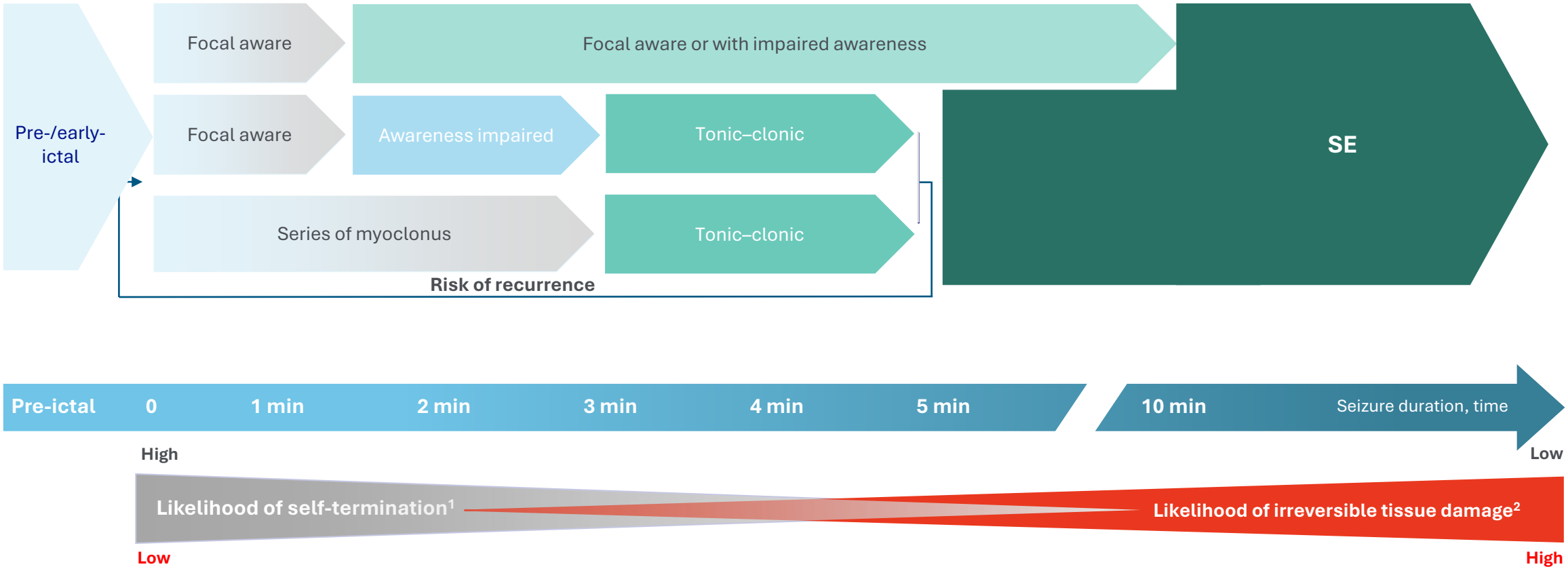
The current seizure emergency treatment journey



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

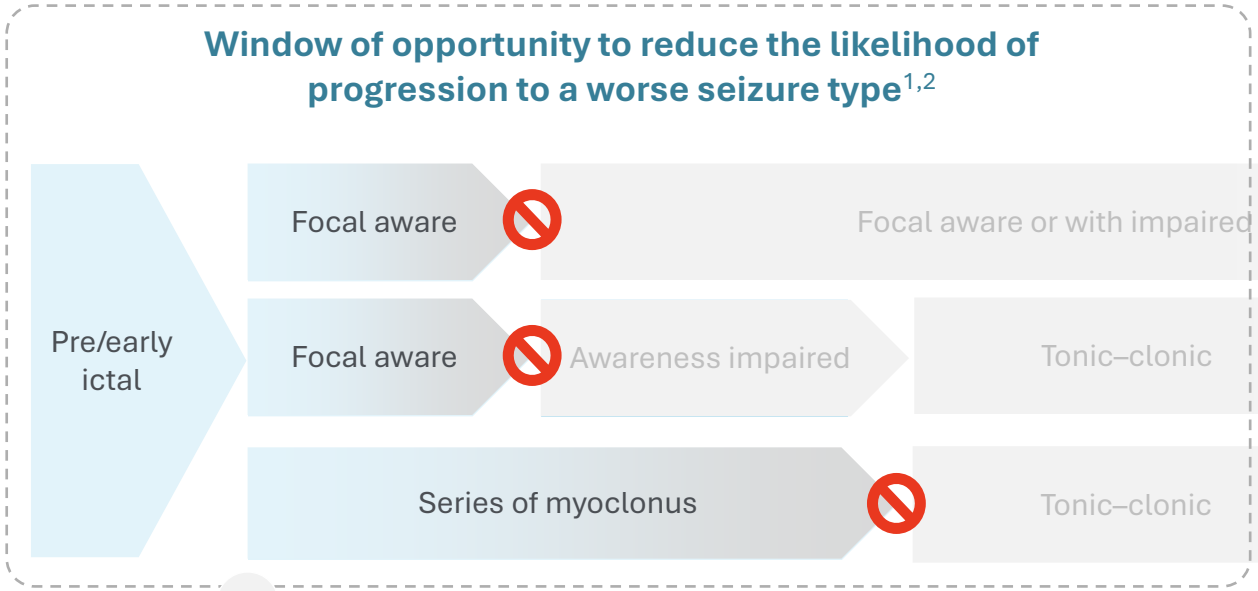
1. Asnis-Alibozek A, et al. *Epilepsy Behav Rep*. 2021;15:100409. 2. LIBERVANT® (diazepam) buccal film PI. https://aquestive.com/content/uploads/libervant-2-to-5-years-of-age-pi-clean-pdf.pdf Accessed March 28, 2025. 3. Betjemann JP, et al. *JAMA*. 2019;321(12):1216-1217. 4. emDocs. Treatment of seizures 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)



There is a **short window of opportunity to stop seizures before progression** to impaired awareness (1 min), FBTCS (1.6 min) or tonic–clonic SE (5 min)[1,5-7]

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.

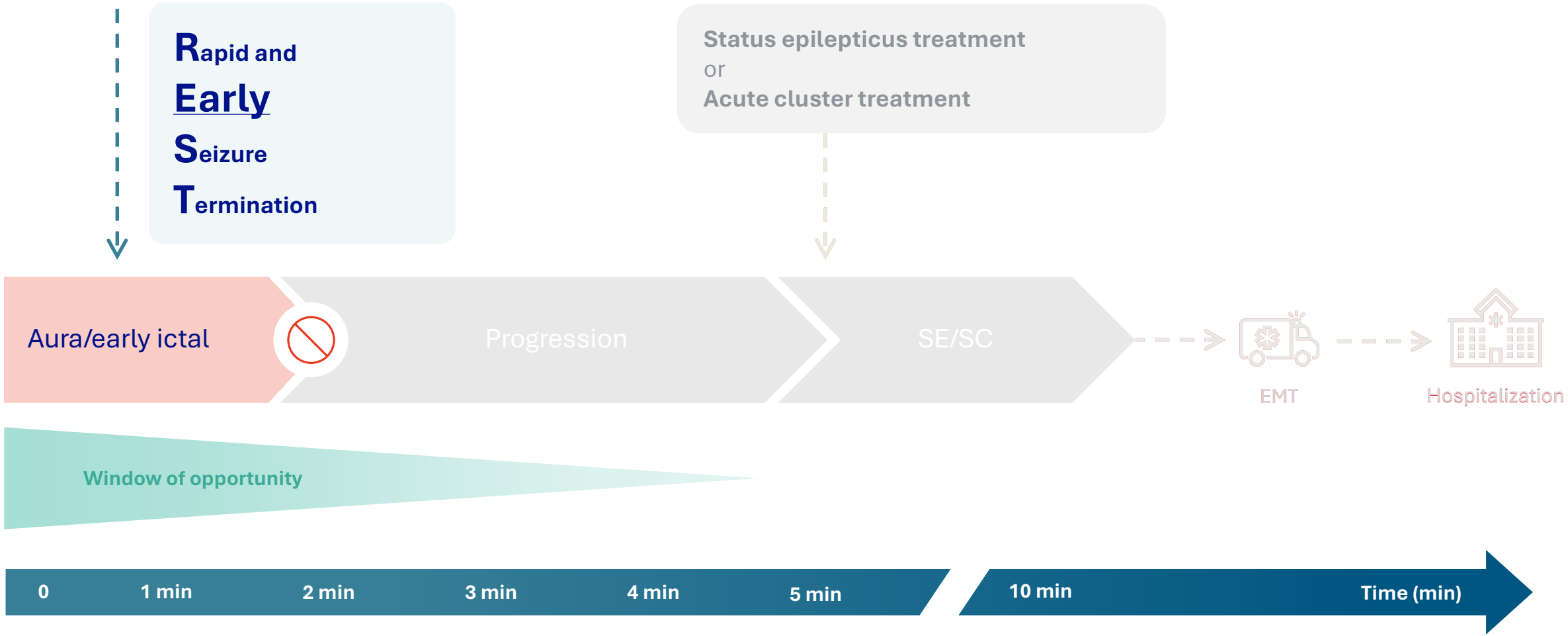
The evolving treatment paradigm: Rapid and Early Seizure Termination (REST)

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

Pina-Garza JE, et al. *Epileptic Disord*. 2024;26(4):484-497.

Seizure emergencies: prevention instead of “rescue”?



EMT, emergency medical technician; IV, intravenous; REST, Rapid and Early Seizure Termination; SC, seizure cluster, SE, status epilepticus.
Asnis-Alibozek A, et al. *Epilepsy Behav Rep*. 2021;15:100409.

When to administer treatment? REST vs ACT

When should REST be administered?

REST

As EARLY as possible when onset recognizable

Prolonged seizure

92%

Seizure onset

When should ACT be administered?

ACT

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

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

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

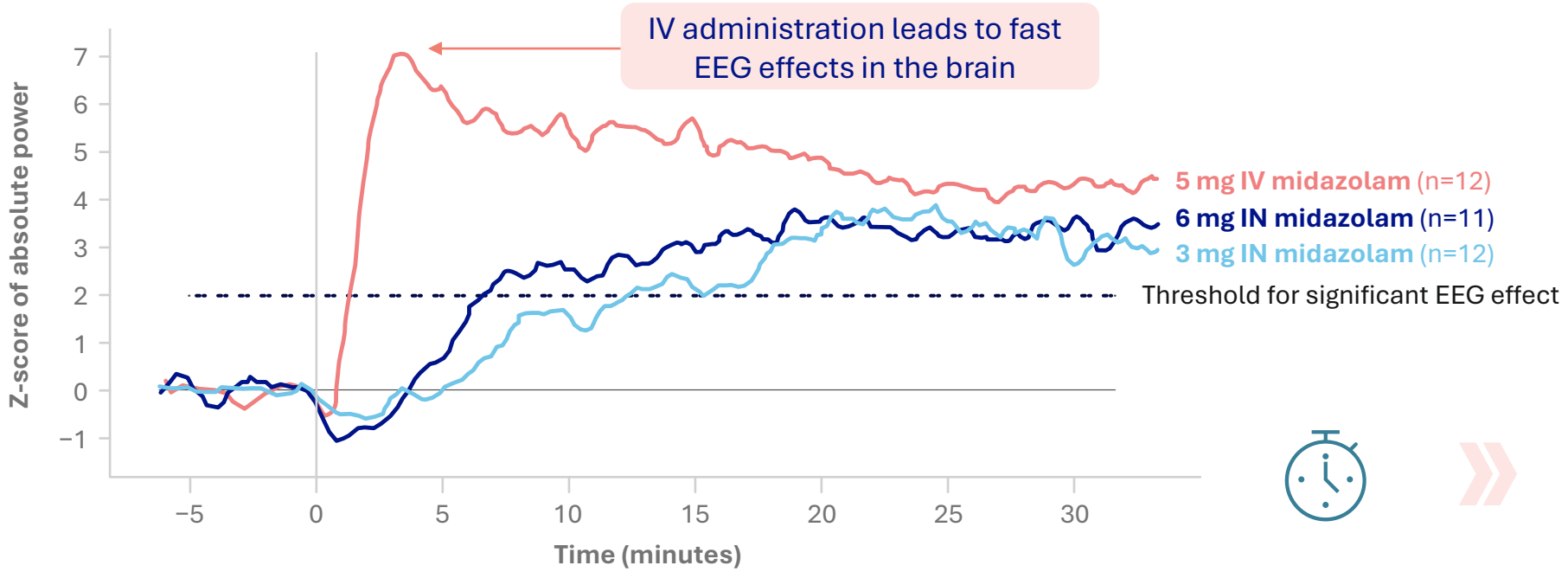
The material presented may contain unapproved indications and/or use and/or products. Licenses may vary by country. Please always refer to the prescribing information in your country before prescribing any drug.

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. KLONOPIN® (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 β1 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 β2 band (18–25 Hz) as a central pharmacodynamic marker as a proxy for time to onset of action.

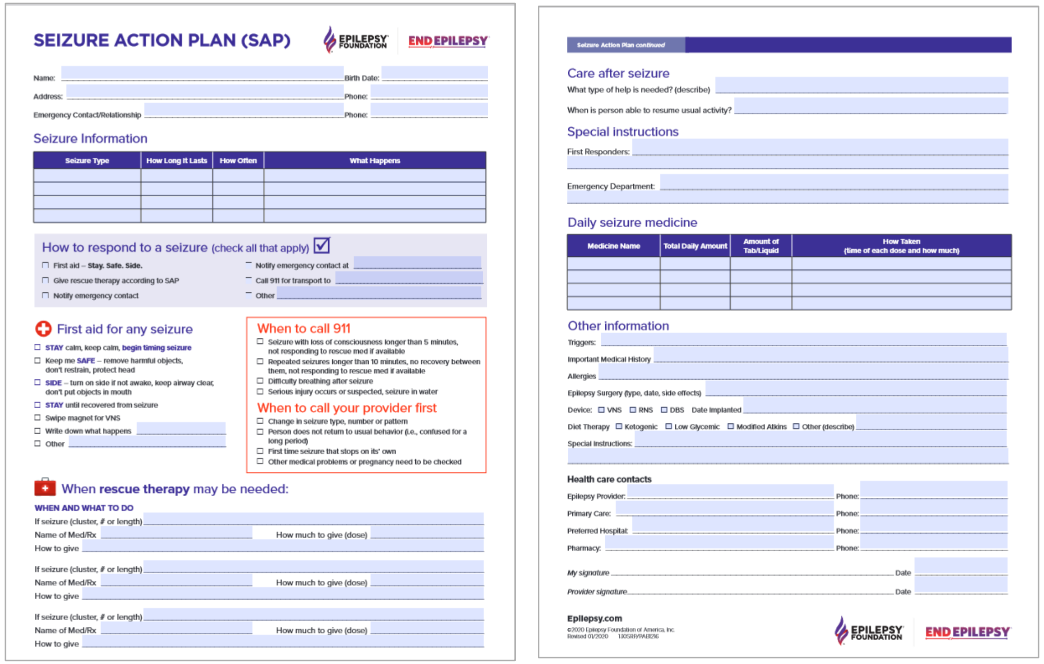
β1, beta 1; β2, beta 2; EEG, electroencephalogram; Hz, hertz; IN, intranasal; IV, intravenous; SD, standard deviation.

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

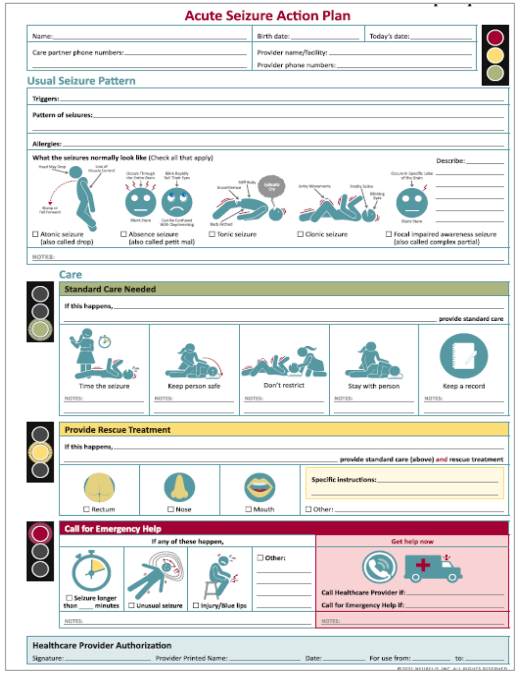
Building seizure duration into the seizure action plan discussion

Understanding of specific seizure emergencies may allow an individualized approach to the recommendation for rescue treatment according to patient presentation and type of seizure emergency[1]

Seizure action plan (SAP)[2]



Acute seizure action plan (ASAP)[3]



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

Pina-Garza JE, et al. *Epileptic Disord*. 2024;26(4):487-497.

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

Questions?