SEIZE YOUR POTENTIAL: MEDICAL MANAGEMENT OF EPILEPSY AND STATUS EPILEPTICUS

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Disclosures

- Relevant Financial Conflicts of Interest
  - None

- Off-Label uses of Medications
  - Status Epilepticus: cyclophosphamide, IVIG, ketamine, lacosamide, levetiracetam, magnesium, midazolam, prednisolone, propofol, rituximab, topiramate, valproic acid

At the conclusion of this activity, pharmacists should be able to successfully:

- Describe the basic pathophysiology of epilepsy
- Compare the mechanisms of action, drug interactions, and adverse effects of the most common antiepileptics
- Apply medication-related principles and patient-related factors to determine appropriate epilepsy therapy options for adult and pediatric patients

At the conclusion of this activity, technicians should be able to successfully:

- Describe safe handling practices for all hazardous antiepileptics
- Identify which antiepileptics are controlled substances and determine their corresponding schedules
- Apply hazardous drug information to determine how to properly dispose of antiepileptic medications

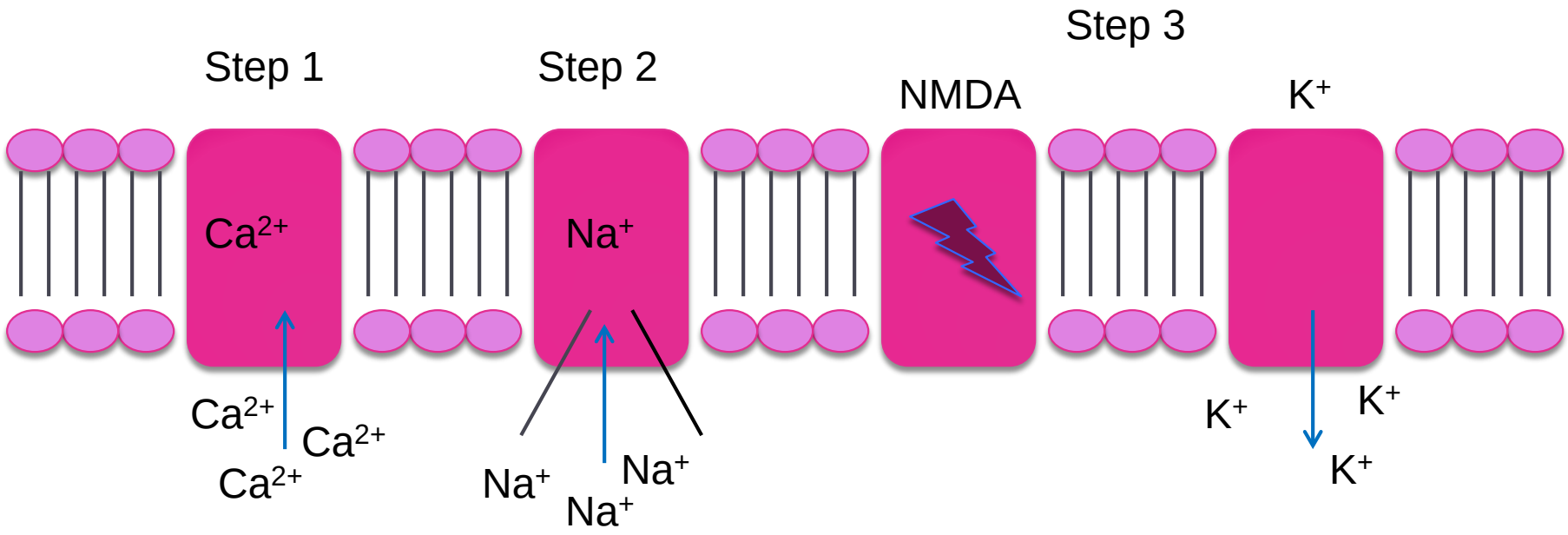
Definitions

- Seizure: paroxysmal event due to excessive or synchronous neuronal brain activity
  - Caused by abnormal balance of excitation and inhibition in the CNS
  - Range from convulsive to absence

- Epilepsy: disorder of chronic hyperexcitability leading to recurrent seizures

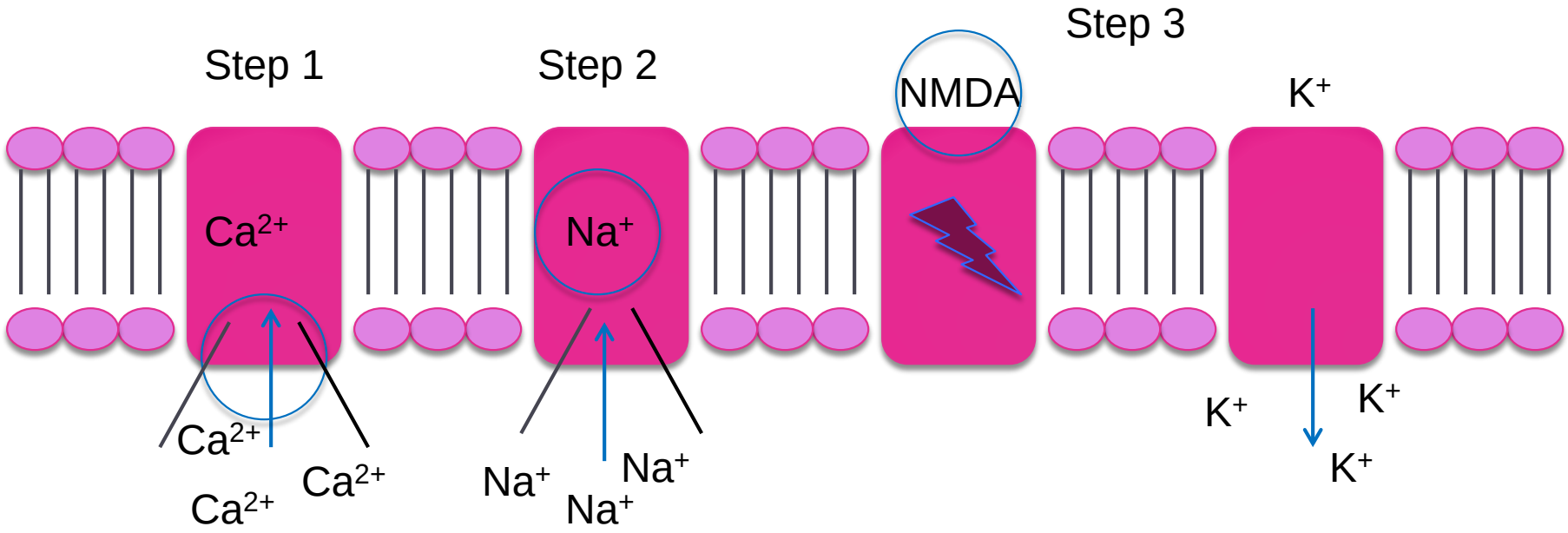
Pathophysiology of Epilepsy

- Seizure initiation and propagation
  - Initiation: 2 concurrent events occur in multiple neurons
    - High-frequency bursts of action potentials (Steps 1&2)
    - Hypersynchronization (Step 3)



Where do the medications work?

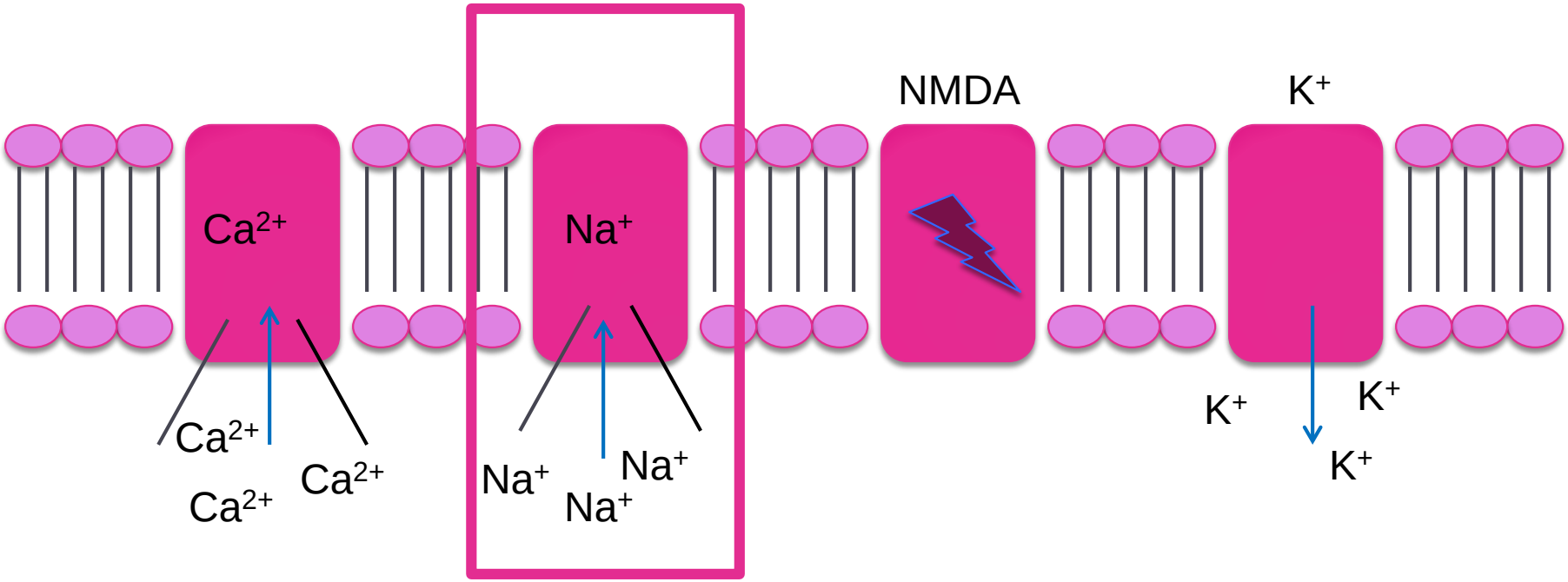
- Seizure initiation and propagation
  - Initiation: 2 concurrent events occur in multiple neurons
    - High-frequency bursts of action potentials (Steps 1&2)
    - Hypersynchronization (Step 3)



Most Common Antiepileptics to Review

- Sodium Channel Inhibitors
- GABA Enhancers
- Calcium Channel Inhibitors/other unique mechanisms

Sodium Channel Inhibitors



Sodium Channel Inhibitors: Clinical Pearls

- **Carbamazepine**
  - Inducer and auto-inducer
  - Adults may require 1.6-2.4 g/day (max: 1600 mg/day)
  - HLA-B*1502:↑ risk SJS; HLA-A*3101:↑ risk hypersensitivity
- **Eslicarbazepine**
  - Active metabolite: Oxcarbazepine
  - Can start 800 mg daily if seizure risk > ADR
  - Hyponatremia/hypochloremia can occur 3 days into treatment
- **Oxcarbazepine**
  - Inducer, no auto-induction
  - 25-50% cross-sensitivity to carbamazepine

All have risk of hyponatremia (often within first 3 months)

Sodium Channel Inhibitors: Clinical Pearls

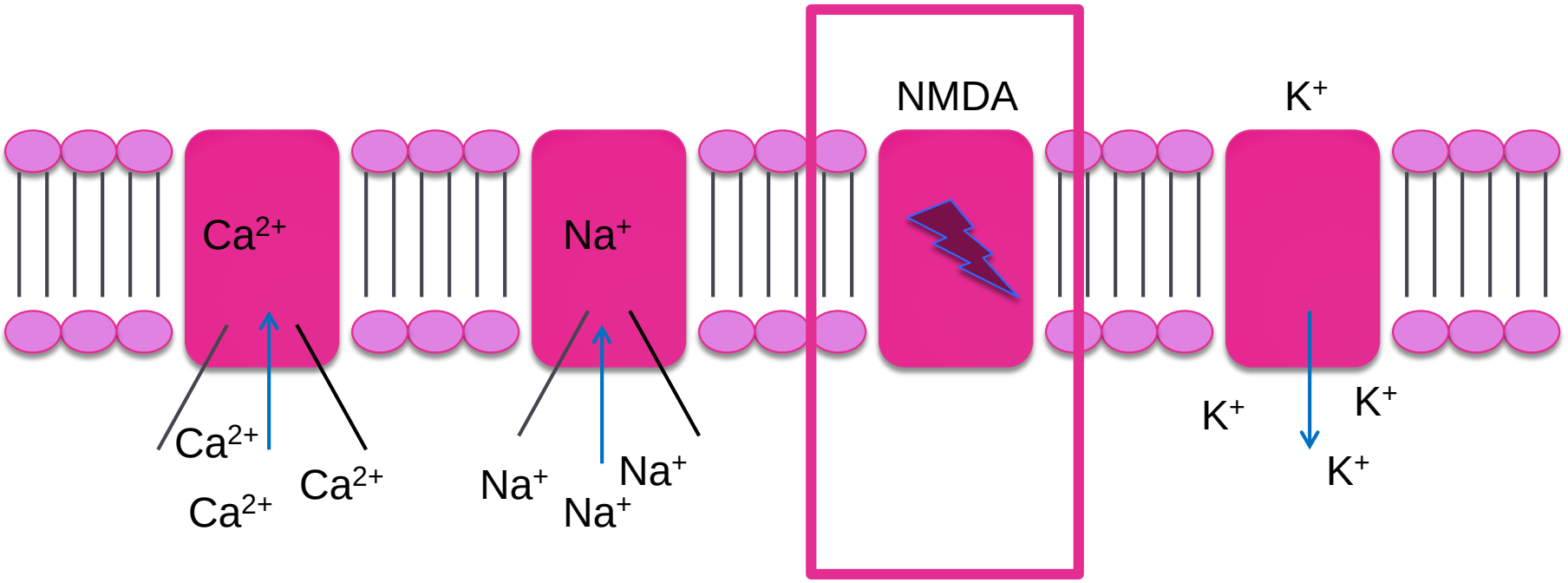
- **Lacosamide**
  - Monotherapy: start 100 mg BID (if adjunct, start 50 mg BID)
  - Minimal ADEs, but dosing often limited by dizziness

- **Lamotrigine**
  - FDA-labeled dose adjustments: ↓ with VPA; ↑ with CBZ, phenytoin, phenobarbital
  - ADEs in children: tics, ↑ risk of SJS/TEN

- **Fosphenytoin**
  - Advantages over phenytoin: IV or IM, minimal extravasation/phlebitis, infuse 150 mg phenytoin equivalents (PE)/min, use NS or D5W

- **Phenytoin**
  - 1.5 mg fosphenytoin = 1 mg phenytoin = 1 mg PE
  - 95% protein bound

GABA Enhancers

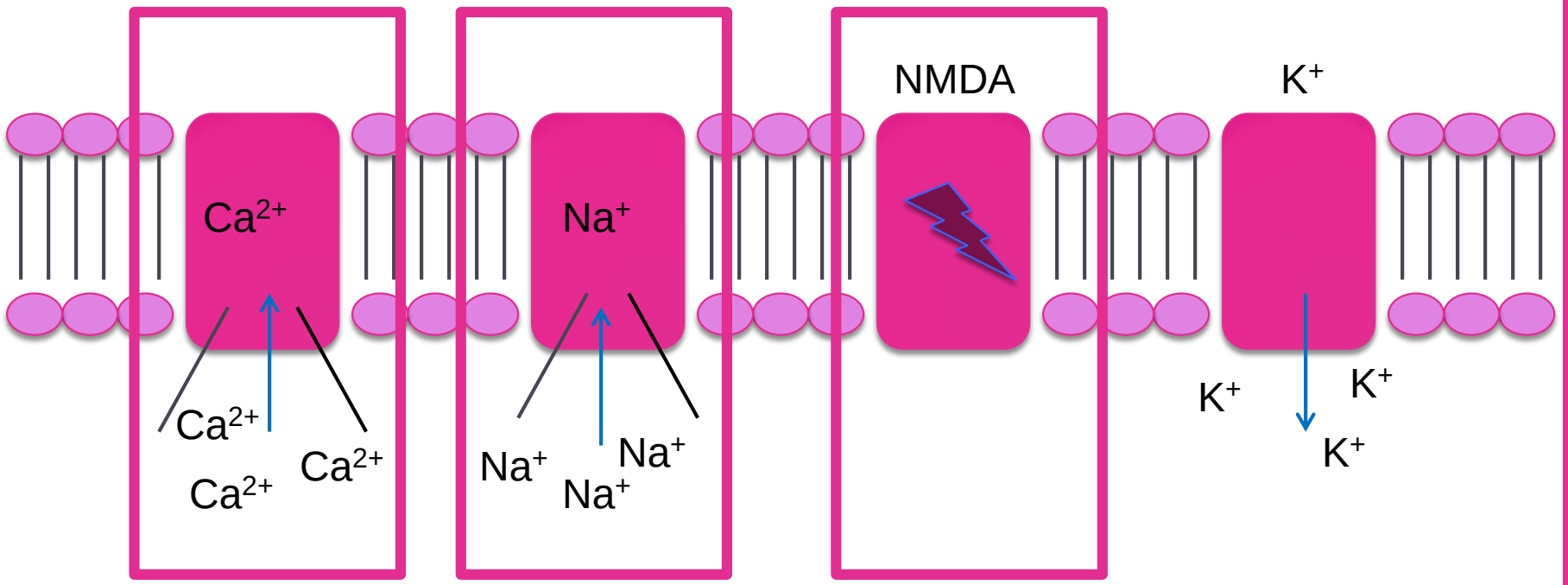


GABA Enhancers: Clinical Pearls

- **1,4-Benzodiazepines**
  - e.g. alprazolam, clonazepam
  - Used PRN for seizures
  - Usually sedating

- **Phenobarbital**
  - ½ life: ~79 hours
  - Titrating on and off usually takes at least 6 months
  - Used frequently in pediatrics, especially NICU
  - Obtain DEXA scans and Vitamin D levels regularly

Other Antiepileptics



Other Antiepileptics: Clinical Pearls

- **Levetiracetam**
  - MOA: prevents hypersynchronization of epileptiform bursts & propagation of seizures by binding to synaptic vesicle protein SV2A & ↓ Ca^{2+} currents
  - "DIVORCE PILL!" in adults – treat with pyridoxine
  - " Keppra Crazies"*

- **Topiramate**
  - MOA: Na^{+} and Ca^{2+} channel blocker, ↑ GABA, ↓ glutamate, ↓ carbonic anhydrase
  - Decreased sweating*
  - Impaired memory*

*Concern especially in pediatrics

Other Antiepileptics: Clinical Pearls

- **Valproic acid**
  - MOA: Inhibits T-type Ca^{2+} currents and Na^{+} channels, ↑ GABA production
  - Conversion from Depakote to Depakote ER: may require ↑ in TDD ~8-20%
  - Long-term high-dose or acute overdose induces carnitine depletion

- **Zonisamide**
  - MOA: Na^{+} and Ca^{2+} channel blocker
  - Decreased sweating*
  - Contraindications: CrCl <50 mL/min , sulfa allergy

*concern especially in pediatrics

New Antiepileptics

- Clobazam (Onfi®)
- Brivaracetam (Briviact®)

Clobazam (Onfi®)

- MOA: GABA-A enhancer (1,5-benzodiazepine)
- Indicated in Lennox-Gastaut syndrome
- Dosing NOT PRN: 5 mg BID for 1 week, then 10 mg BID for 1 week, then 20 mg BID
  - Max dose if ≤2 years old: 10 mg/day
  - Max dose if 2-16 years old: 40 mg/day

Can see much higher in practice!

- PK: CYP3A4/2C19 substrate; adjust dose in renal and hepatic failure
- Adverse Effects:
  - Dose-related: sedation, irritability, drooling, aggression
    - Less sedating than other benzodiazepines (because 1,5)

Brivaracetam (Briviact®)

- MOA: binds to synaptic vesicle protein SV2A in brain (10-fold higher affinity than levetiracetam)
- Adjunctive therapy for refractory partial onset seizures in adults
  - Not used much in pediatrics yet
- Dosing: 50 mg PO BID, adjust to 25 mg or 100 mg BID if needed due to side effects/ineffectiveness
  - Adjust in any degree of hepatic dysfunction (max: 75 mg PO BID)
- PK: weakly inhibits CYP2C19, substrate of CYP2C9/2C19

Brivaracetam (Briviact®)

- Common Adverse Effects: hypersensitivity reactions, somnolence and sedation, dizziness, nausea, vomiting, fatigue
- Warnings: psychiatric, neurologic, and hematologic events, and the potential for abuse
- Hazardous Drug Information:
  - Controlled substance: V
  - Proper disposal: N/A

Brivaracetam (Briviact®)

- Lattanzi et al, 2016: Meta-analysis of 6 parallel double-blind, placebo-controlled RCT
- Population: > 16 years old with partial onset seizures uncontrolled with > 1 AED
- Results
  - > ↓50% in seizure frequency compared with baseline: brivaracetam RR 1.79 (95% CI 1.51-2.12)
  - No seizures during treatment period: brivaracetam RR 4.74 (95% CI 2-11.25)

Epilepsy Treatment Considerations

- Seizure type
- Mechanism of action
- Comorbidities (hepatic/renal failure, hyponatremia)
- Adverse reactions (dose-related v. idiosyncratic)
- Drug interactions
- Compliance
- Cost

Epilepsy Treatment After First Unprovoked Seizure

- Pediatrics
  - Evidence from studies is weak
  - Common ADEs: changes in behavior and cognitive function
- Adults
  - Incidence of AED-related adverse effects 7-31%
  - Newer agents show ↓ AED-related adverse effects
- Both
  - Recurrence usually occurs within first 1-2 years
  - Recurrence lower in those treated with an AED
  - Sustained seizure remission not affected by immediate AED initiation

Case 1

JM is a 16-year-old male with recurrent epilepsy. He has been taking levetiracetam for 1 year and has not had a seizure since. He has no other conditions and takes no other medications. Both him and his mother want to switch medications because he has become intolerable at home. He participates in sports year-round, but has recently fought with other teammates and is suspended from the team. Which of the following is the best choice for pharmacologic management of JM's epilepsy?

A. Fosphenytoin

B. Brivaracetam

C. Topiramate

D. Decrease dose of levetiracetam

Drug Safety Information

- NIOSH group 2
  - Carbamazepine (Tegretol®)
  - Divalproex (Depakote®)
  - Fosphenytoin (Cerebyx®)
  - Oxcarbazepine (Trileptal®)
  - Phenytoin (Dilantin®)

NIOSH group 3

- Clonazepam (Klonopin®)
- Eslicarbazepine (Aptiom®)
- Topiramate (Topamax®)
- Valproic acid (Depakote®)
- Zonisamide (Zonegran®)

Antiepileptic Controlled Substances

- Benzodiazepines: Schedule IV
- Brivaracetam: Schedule V
- Lacosamide: Schedule V
- Phenobarbital: Schedule IV

Proper Disposal of Antiepileptics

- No specific disposal information for antiepileptics
- Follow proper procedures for wasting controlled substances at individual facility
- Inpatient:
  - Nurses "waste" all controlled substances that are not used within the Omnicell or other medication management technology
  - Pharmacy: logs "waste" into Controlled Substances Manager (i.e. Omnicell) and will generally put substance into an isolyzer

Major Drug Interactions

Hepatic Enzyme	Substrate	Inducer	Inhibitor
CYP2C9	**Fosphenytoin, phenytoin**	Carbamazepine, fosphenytoin, phenobarbital, phenytoin	**Valproic acid**
CYP2C19	Clobazam, fosphenytoin, phenobarbital, phenytoin	Carbamazepine, fosphenytoin, phenytoin	
CYP3A4	Carbamazepine, zonisamide	Carbamazepine, fosphenytoin, phenobarbital, phenytoin	

If starting a medication that interacts, dose adjustments or additional monitoring may be needed

Major Drug Interactions

- Common medications altered by AED enzyme inducers
  - Anti-hypertensives
  - Cholesterol-lowering medications
  - HIV medications
  - Hormonal contraception
  - Solid organ transplant medications
  - Tuberculosis medications
  - Warfarin

Antiepileptic Therapeutic Concentrations for Adults and Pediatrics

Medication	Therapeutic Concentration
Carbamazepine	4-12 mcg/mL
Clobazam	100-300 mcg/L
Levetiracetam	12-46 mcg/mL
Phenobarbital	15-40 mcg/mL
Phenytoin	Total: 10-20 mcg/mL Free: 1-2 mcg/mL
Valproic acid	50-100 mcg/mL

Note: target concentrations may be higher or lower depending on the patient.

Caution: monitor and adjust doses regularly for weight changes in pediatrics

*Adjustment of phenytoin **Total** levels:
Corrected Phenytoin = Measured Phenytoin Level / ([adjustment factor *albumin] + 0.1

Adjustment Factor for Low Albumin: 0.2
Adjustment Factor for CrCl <10 mL/min or dialysis: 0.1

Case 2

A patient's antiepileptic levels come back on Day 7 of hospitalization. His valproic acid level is low (33 mcg/mL) and adjusted total phenytoin is high (23.1 mcg/mL). Why could this be?

Case 2 Answer

- Drug-drug interaction between valproic acid and Phenytoin
  - Valproic acid displaces phenytoin from protein binding sites
  - Phenytoin increases degradation of valproic acid

Special Populations

- Children and Adults with Refractory Seizures
  - Ketogenic diet
- Pregnancy

Ketogenic Diet

- Etiology in seizure cessation unknown
  - Ketone bodies have neuro-protective properties
  - Reduction in hyperexcitability

- High-fat, very low carbohydrate diet
  - Mimics body's response to starvation
  - Shifts brain metabolism to ketones

- Carbohydrates allowed in 1000 calorie diet
  - 8 g carb on 4:1 diet
  - 16 g carb on 3:1 diet
  - 30 g carb on 2:1 diet
  - 40-60 g carb on 1:1 diet

Ketogenic Diet

- Efficacy
  - 2006 meta-analysis of 19 studies: 1084 patients after 6 months on diet
    - 60% had 50% seizure reduction
    - 30% had >90% seizure reduction
  - RCT: 145 children 2-16 years old
    - 28 on diet and 4 in control had >50% seizure reduction

- Safety
  - Adverse effects: nausea, vomiting, constipation, dehydration, hypercholesterolemia, hypoglycemia, kidney stones, lethargy, osteopenia, slowed growth
  - Severe: acidosis, hyperventilation

Pharmacist Role in Ketogenic Diet

- All medications NTE >1 g carbohydrates
  - Look for "carbohydrate free", not "sugar free"
  - Liquids and suspensions usually contain carbohydrates
- IV medications: Do not dilute in dextrose
- TPNs
  - Lipids 3 g/kg restriction
  - Include glycerol in lipid carbohydrate calculation
- Medication interactions with ketogenic diet
  - Acetazolamide: metabolic acidosis
  - Phenobarbital: ↑ serum levels and sedation
  - VPA: interferes with ketone production, carnitine deficiency

Low Carb and Carb-Free. The Charlie Foundation. Website: https://www.charliefoundation.org.

Pregnancy

- If possible, plan ahead!
- Monotherapy recommended
- Use lowest possible dose
- Higher folic acid 3-4 mg/day may be recommended for preventing major congenital malformations
- Pregnancy Categories
  - Category C: brivaracetam, clobazam, eslicarbazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, zonisamide
  - Category D: carbamazepine, fosphenytoin, phenobarbital, phenytoin, topiramate, valproic acid

STATUS EPILEPTICUS

Etiology of Status Epilepticus

- Repeated seizures cause synaptic membrane of GABA (inhibitory) to be completely inactivated
- NMDA is upregulated on the neuronal cell membrane, increasing glutamate (excitatory) production and release
- All mechanisms to suppress seizure activity fail leading to persistent seizure activity

Definition of Status Epilepticus

5 minutes or more:

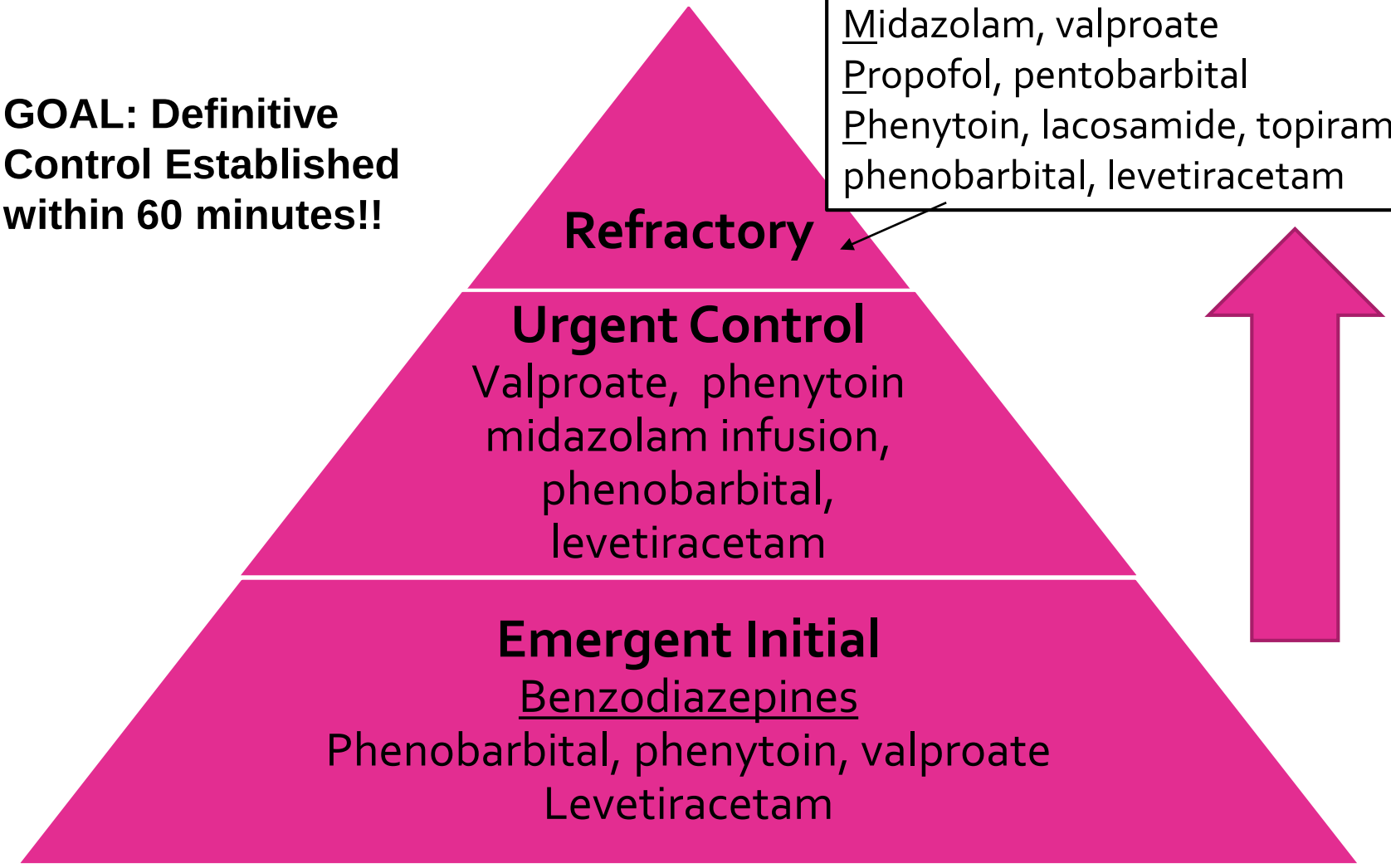
- Continuous clinical and/or electrographic seizure activity

OR

- Recurrent seizure activity without recovery between seizures

Hierarchy of Status Epilepticus Treatment

GOAL: Definitive Control Established within 60 minutes!!



Emergent Initial Therapy of Status Epilepticus

- **Benzodiazepines**
  - IV preferred (lorazepam)
  - If need IM, midazolam recommended
    - Effective inpatient and outpatient for pediatrics
  - If need rectal, diazepam recommended

- **Phenobarbital**
  - Preferred in neonates

Urgent Control of Status Epilepticus

Treatment Goals

1. Responded to Initial Emergent Treatment: Rapid attainment of AED therapeutic levels and subsequent maintenance dosing

2. Did not respond to Initial Emergent Treatment: Stop Status Epilepticus

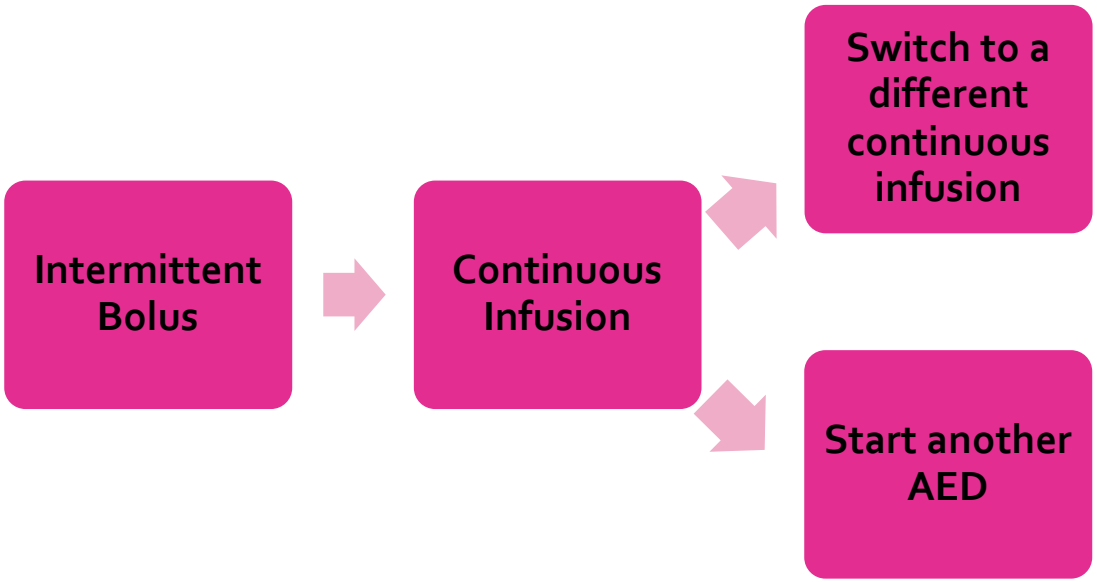
Refractory Status Epilepticus: Which Strategy to Choose?

Consider repeat bolus of urgent control AED

vs.

Immediately initiate additional agents

Refractory Status Epilepticus Treatment Algorithm



- Consider intermittent boluses of valproate sodium, levetiracetam, or phenytoin/fosphenytoin if not previously administered
- Continuous infusion: midazolam, propofol, pentobarbital

Refractory Status Epilepticus Treatment De-escalation

- Seizure control on EEG maintained for 24-48 hours

- Gradually withdrawal the continuous infusion AED
  - If patients have recurrent refractory status epilepticus, titrate the continuous infusion back up

New Strategies for Refractory Status Epilepticus

Adults

- Ketamine
  - NMDA receptor antagonist
- Magnesium
  - Possible NMDA receptor antagonist
- Immunomodulation and corticosteroids
  - Theory: super-refractory status epilepticus caused by antibodies against voltage-gated potassium and NMDA receptors
  - High dose corticosteroids followed by IVIG

Infantile Spasms

- Corticosteroids
- ACTHAR gel (repository corticotropin injection)

Summary

- Epilepsy is a disorder of recurrent seizures
- Treatment choice for epilepsy should be individualized based on patient and medication characteristics
- Status epilepticus is defined by a seizure lasting >5 minutes or recurrent seizure activity without recovery between seizures
- Status epilepticus requires emergent treatment to enhance survival

Claiming Your CE Credit

- https://tshp.wcea.education/homepage
- Pharmacist: d3HA
- Pharmacy Technician: U6z8

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Paradoxical Seizures

- Definition: when an antiepileptic increases the severity or frequency of seizures

- Causes
  - Overdose or Intoxication
  - Tolerance

- Types of Paradoxical Seizures
  - Absence seizures: carbamazepine, phenytoin, phenobarbital (high doses), gabapentin
  - Myoclonus epilepsies: carbamazepine, phenytoin, lamotrigine