

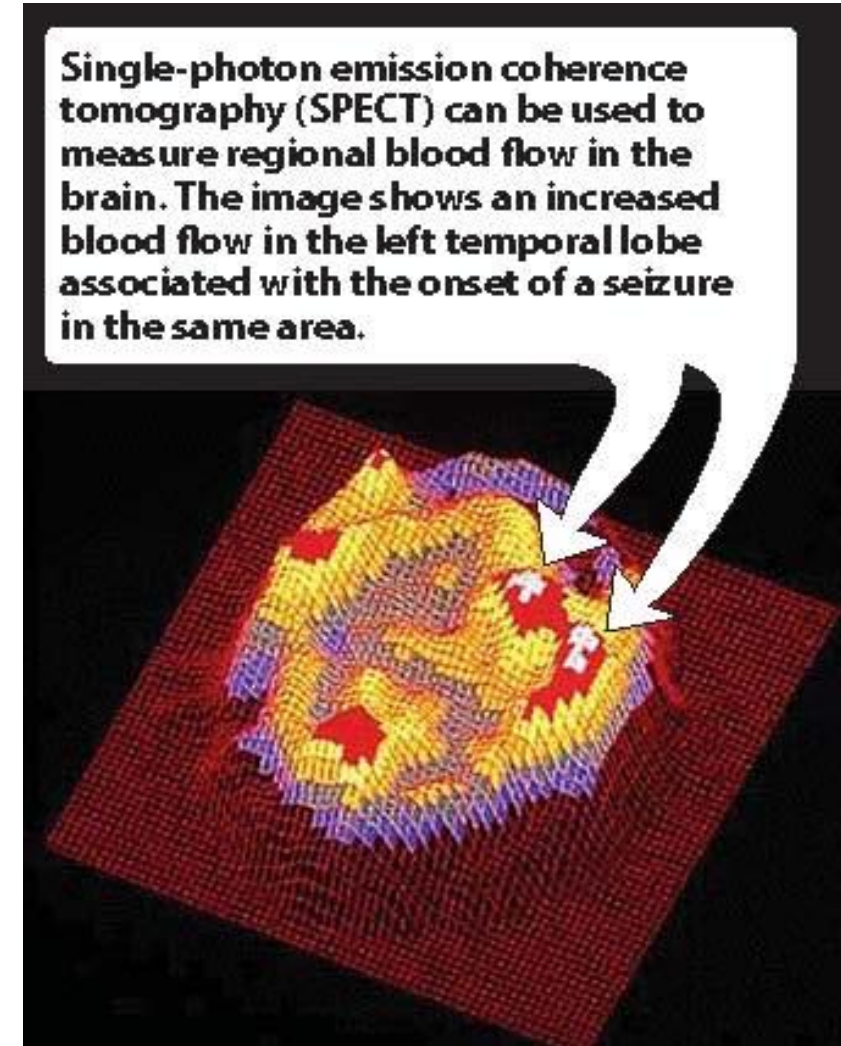


Antiepileptics

Pharmacology and Toxicology
Central Nervous System Module
Third Year Medical Students
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Overview: Epilepsy

- **Seizures**
 - Abnormal excessive neuroactivity in the brain
- **Convulsions:**
 - Rapid, repeated muscle contraction and relaxation resulting from excessive neuroactivity in the brain.
- **Epilepsy:**
 - A neurological disorder of multiple, different seizures resulting from excessive discharge of cerebral neurons.



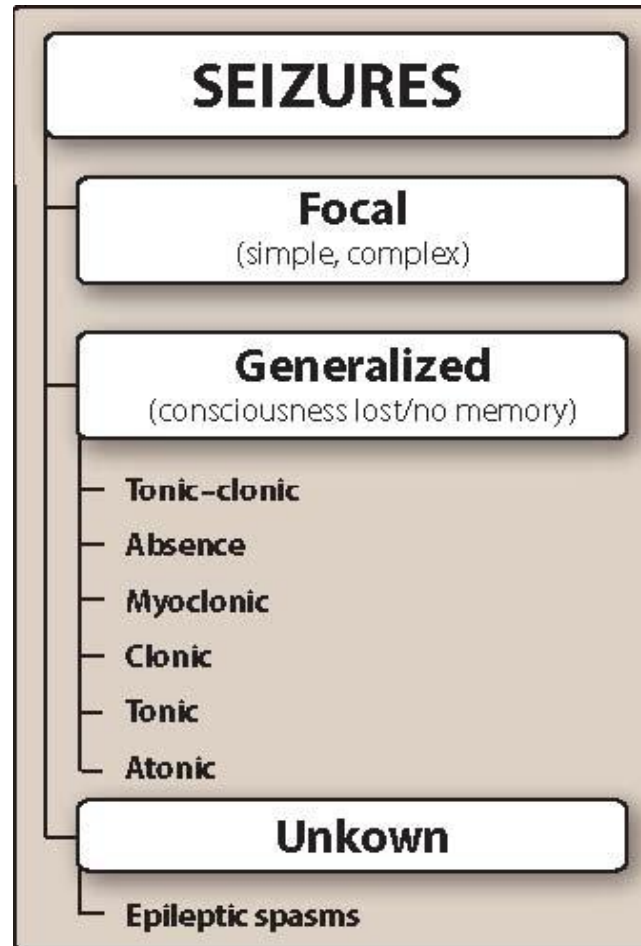


Seizures: Etiology

- Trauma
- Encephalitis
- Drugs
- Withdrawal from depressants
- Tumor
- High fever
- Hypoglycemia
- Extreme acidosis
- Extreme alkalosis
- Hyponatremia
- Hypocalcemia
- Idiopathic

Most cases of epilepsy are idiopathic

Classification of Seizures



Overview: Epilepsy

- **Focal (partial) seizures:**
 - Involves one portion of the brain i.e. one lobe.
 - Symptoms depend on the site of discharge “primary focus”.
 - Possibility of progressing into a generalized tonic-clonic seizure.



Partial seizure

Focal (partial) seizures:

Simple partial

- Confined to a single locus in the brain
- **NO loss of consciousness**
- Single muscle group or a limb

Complex partial

- Consciousness is altered
- Motor dysfunction/hallucination /distortion

Overview: Epilepsy

- **Generalized seizures:**

- Starts at a focal point and spreads to involve both hemispheres.
- Could be convulsive or nonconvulsive.
- Associated with immediate loss of consciousness.



Generalized seizure

Tonic-clonic

- Loss of consciousness
- **Tonic** (continuous contractions) and **clonic** (rapid contraction and relaxation)
- Followed by confusion/exhaustion

Absence

- Brief, abrupt, self-limiting
- Pediatric: 3-5 until puberty
- Starring/rapid-eye blinking
- Characteristic EEG profile

Myoclonic

- Short episodes of muscle contractions i.e., jerks of the limbs

Generalized seizures

Clonic

- Also brief episodes of muscle contraction similar to myoclonic
- Consciousness is more impaired with clonic

Tonic

- Increased muscle tone
- < 60 seconds

Atonic

- Sudden loss of muscle tone “drop attacks”



Epilepsy: Therapeutic Strategy

- “No cure”
- Complete suppression of seizures, or
- Decrease the number of episodes with minimal side effects.

How?

- Pharmacological
- Ketogenic diet
- Surgery/Vagal Nerve Stimulation
- Correct the underlying cause

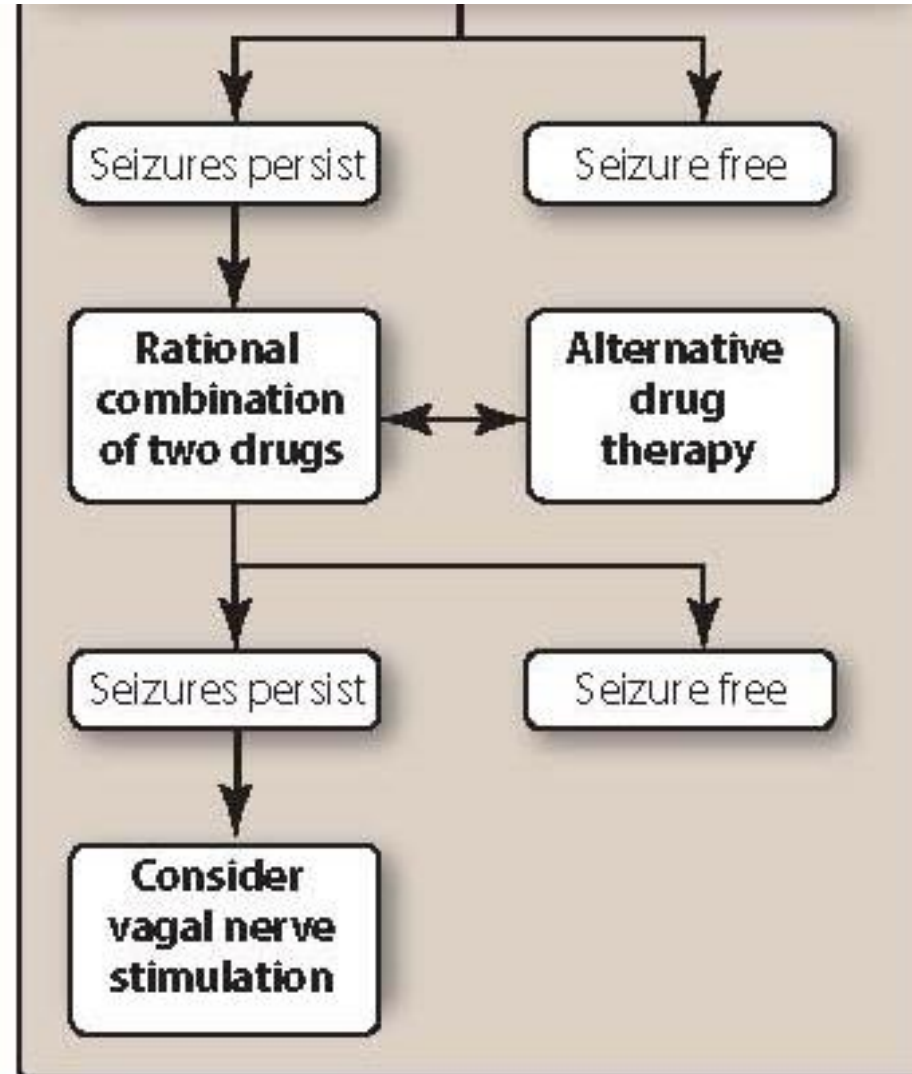
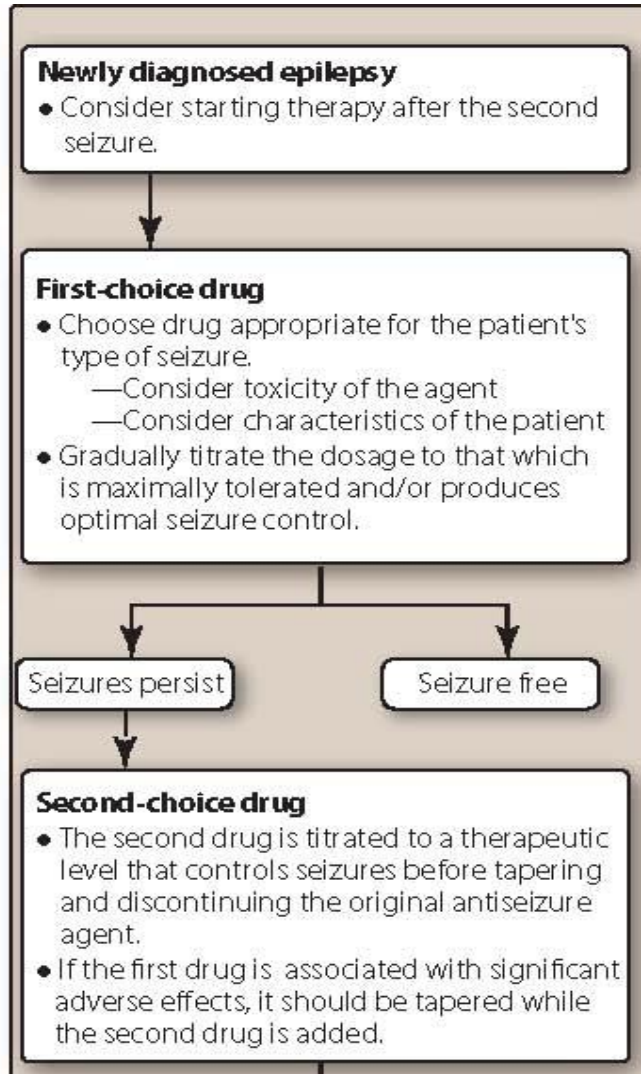


Epilepsy: How to select which drug?

Choice of drug treatment is based on:

- 1- type of seizure
- 2- patient-specific variables (age, comorbidities, lifestyle....)
- 3- characteristics of the drug (cost, adverse effects, interactions...)

Epilepsy: Therapeutic Strategy





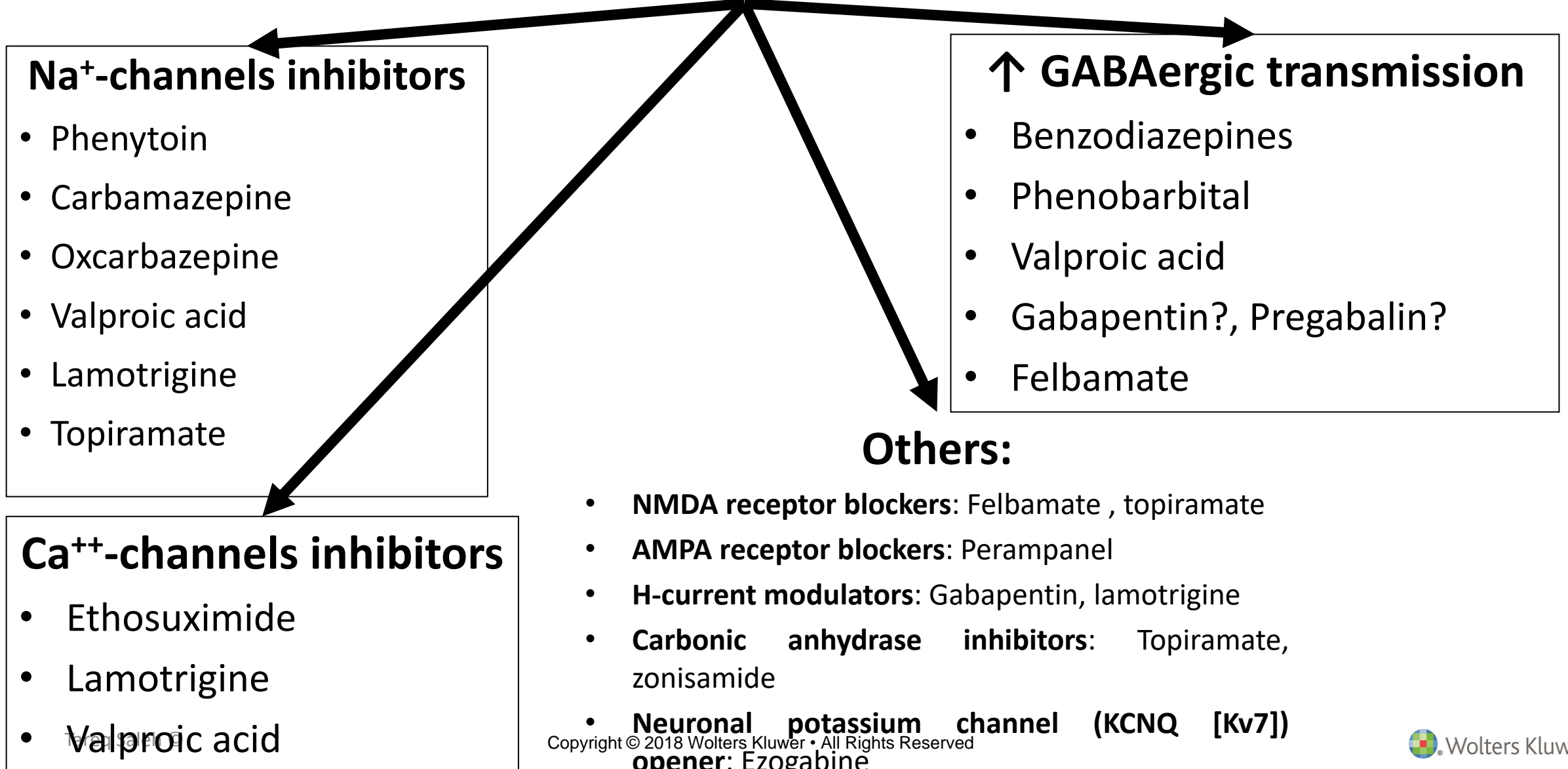
How do antiepilepsy medications work?

Blocking voltage-gated channels (Na^+ or Ca^{++})

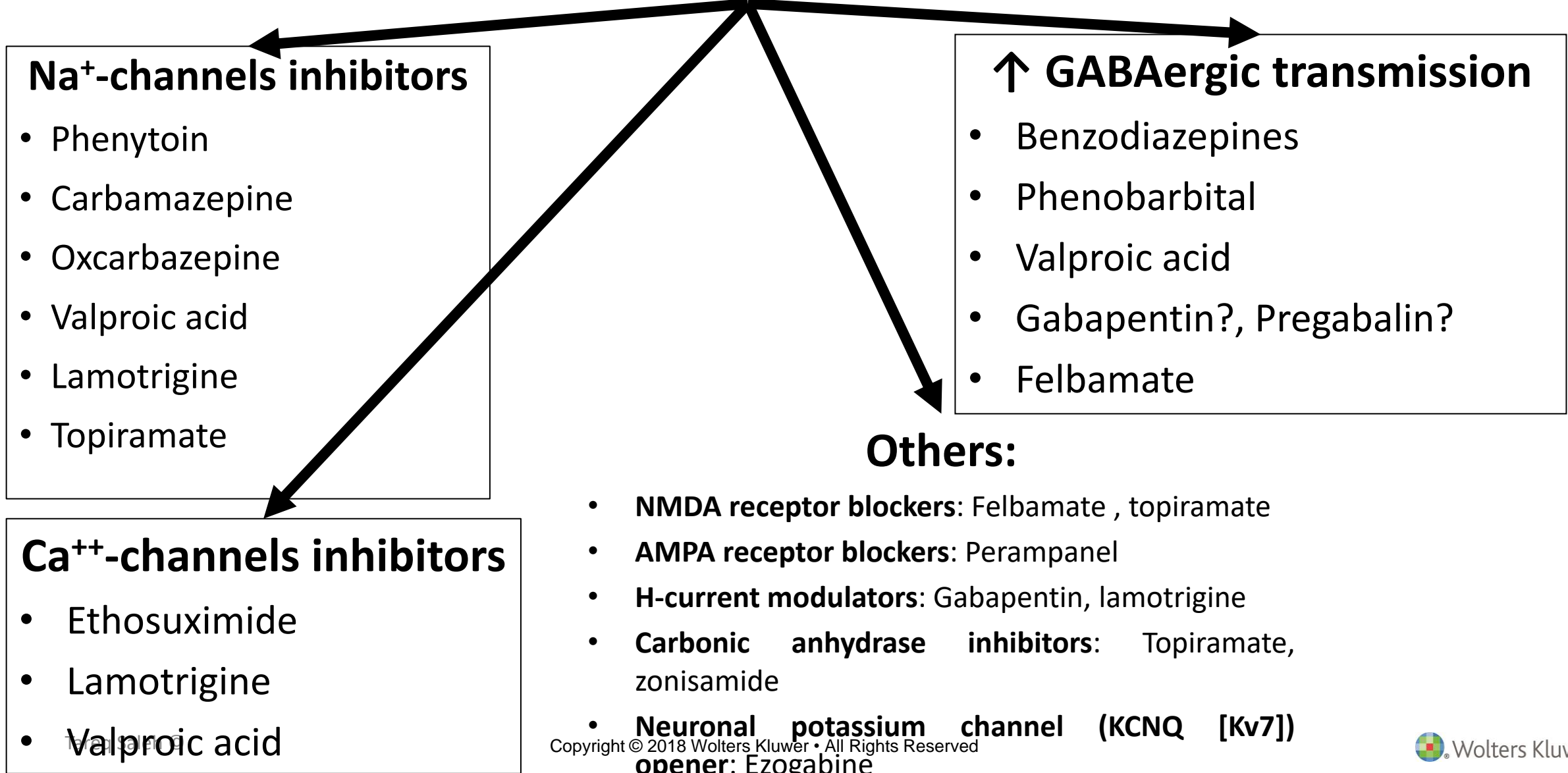
Enhancing inhibitory GABAergic impulses

Interfering with excitatory glutamate transmission

Antiepileptic drugs



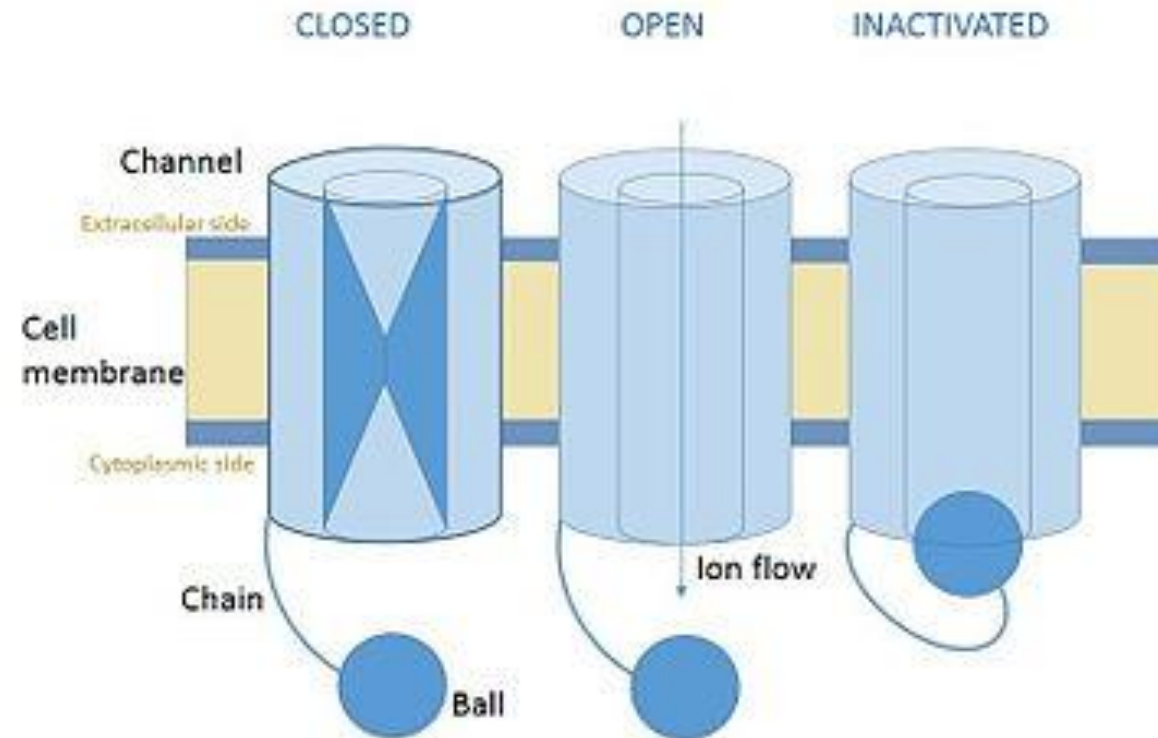
Antiepileptic drugs



MOA:

Blocks voltage-gated Na⁺ channels by binding to inactive state → slow recovery

Phenytoin





Phenytoin

MOA:

Blocks voltage-gated Na⁺ channels by binding to inactive state → slow recovery

Indications:

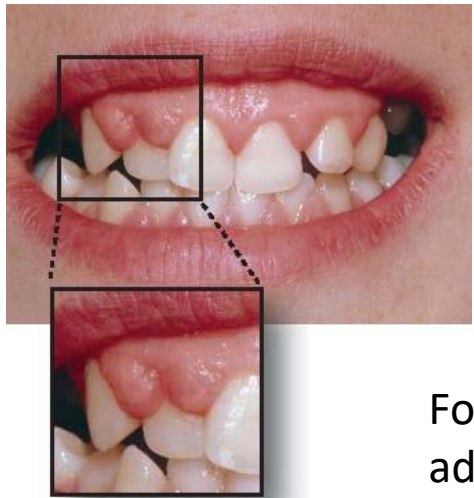
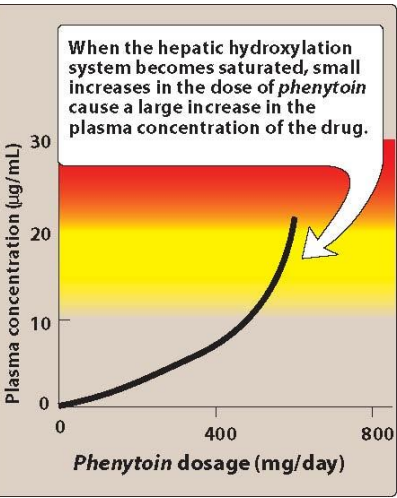
- Focal seizures
- Tonic-clonic
- **NOT** good for absence seizures
- Status epilepticus (after BZD)
- Antiarrhythmic/digoxin toxicity

Adverse effects

- Nystagmus, ataxia
- Diplopia, sedation
- Gingival hyperplasia
- Peripheral neuropathy/osteoporosis
- Teratogenic
- Blood: ↓ folate → Megaloblastic anemia
- Drug-drug interactions: e.g., warfarin

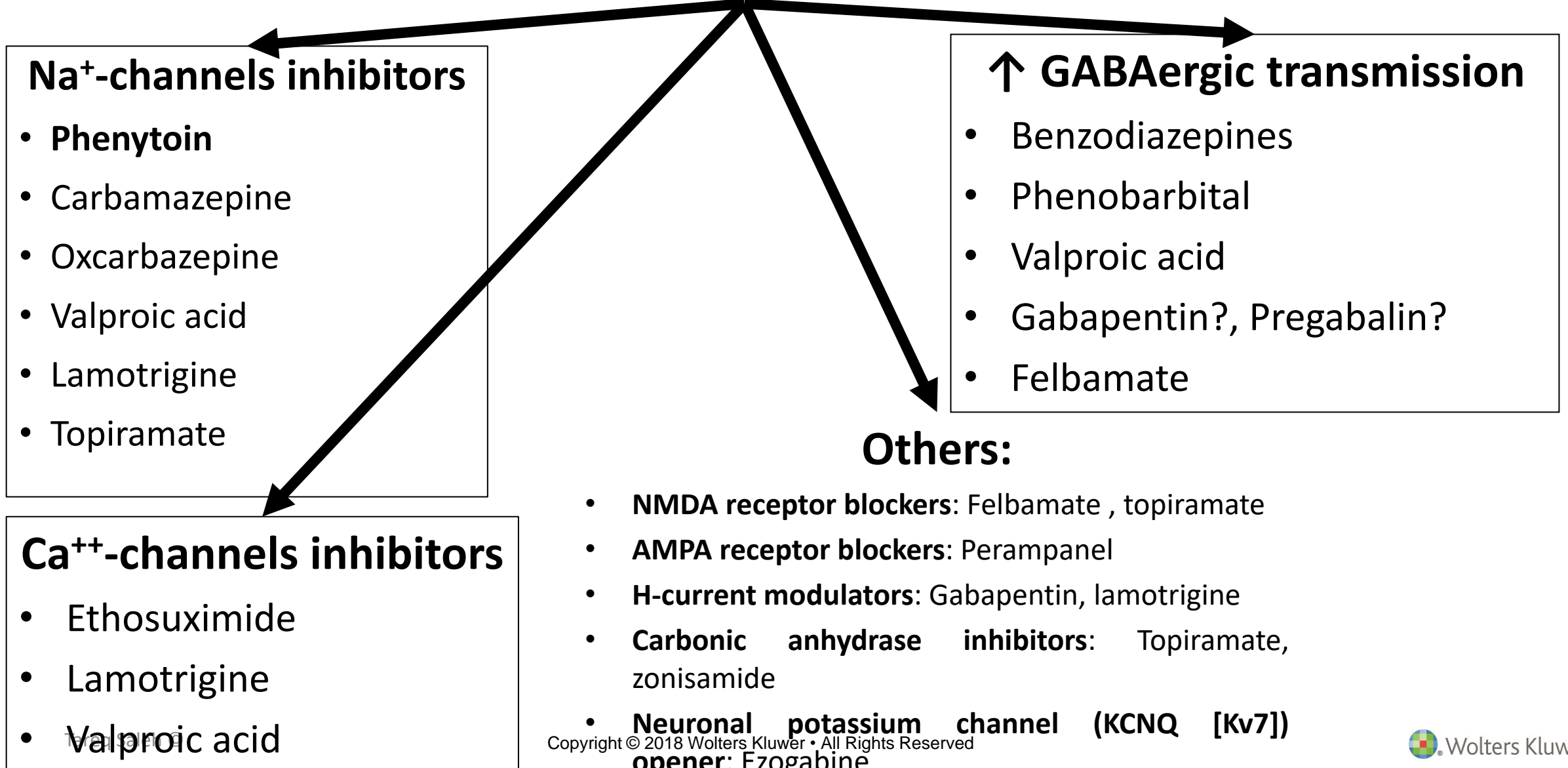
Pharmacokinetics:

- **Induces** CYP2C, CYP3A, UGT
- “saturable enzyme metabolism”
- Non-linear kinetics
- Toxicity



Fosphenytoin for IM administration

Antiepileptic drugs



Carbamazepine

MOA:

Blocks Na⁺ channels

Indications:

- Focal seizures
- Tonic-clonic
- **NOT** good for absence seizures
- Trigeminal neuralgia
- Bipolar disorder

Pharmacokinetics:

- Absorbed slowly
- Long half-life (~ 30 hours)
- **Induces** CYP2C, CYP3A, UGT

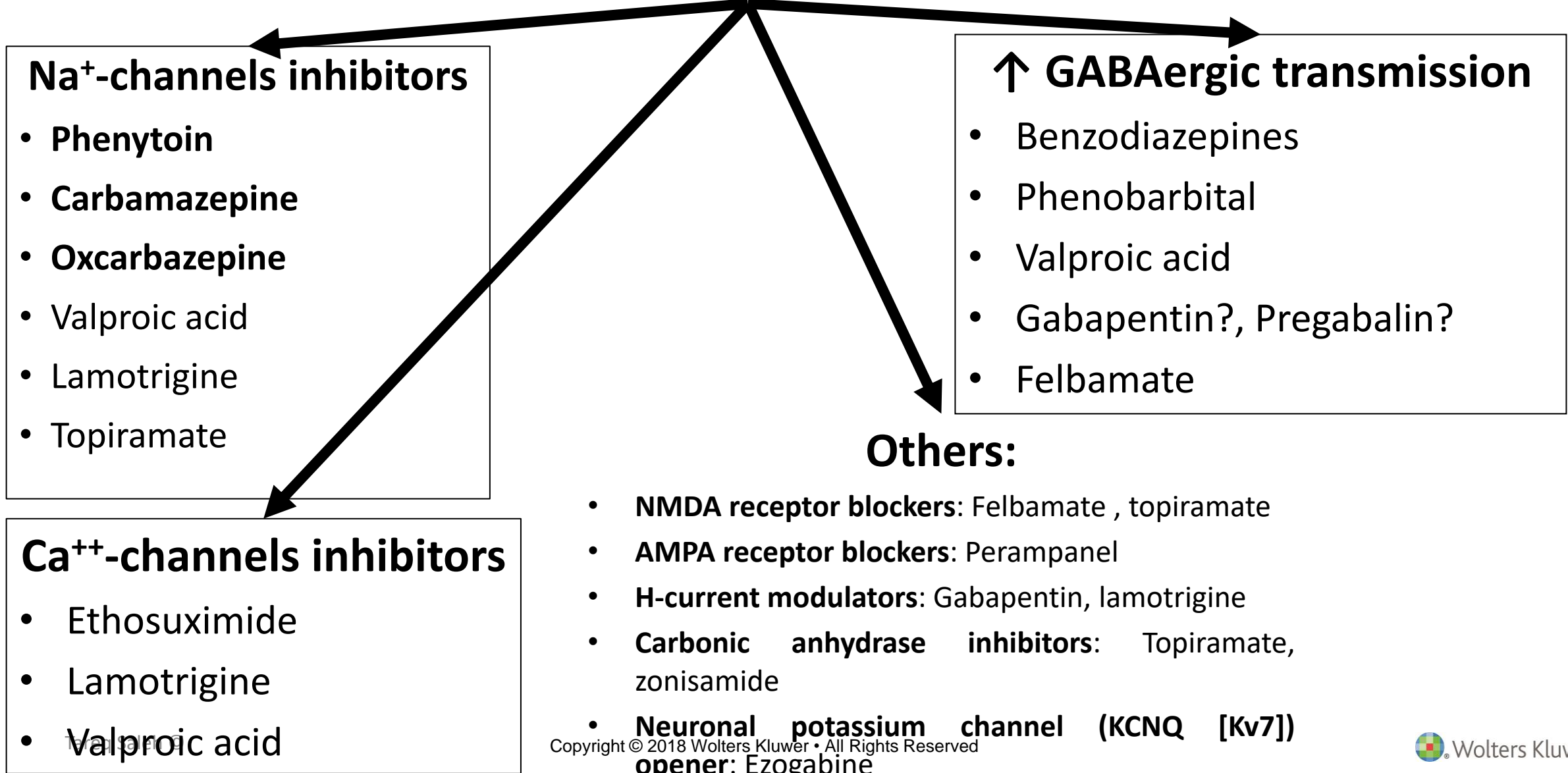
Adverse effects

- Hyponatremia
- Aplastic anemia
- Teratogenic: Spina Bifida
- Drowsiness; headache; dizziness; nausea

Oxcarbazepine

- Prodrug
- Less side effects

Antiepileptic drugs



Valproic acid

MOA:

- Blocks Na⁺ channels
- Blocks GABA transaminase (GABA-T)
- Blocks T-type Calcium channels

Indications:

- Focal seizures
- Generalized seizures
- Absence seizures
- Bipolar disorder

Pharmacokinetics:

- **Inhibits** CYP2C9, UGT, epoxide hydroxylase

Adverse effects

- Hepatotoxicity
- Teratogenicity
- CNS-related

Valproic acid

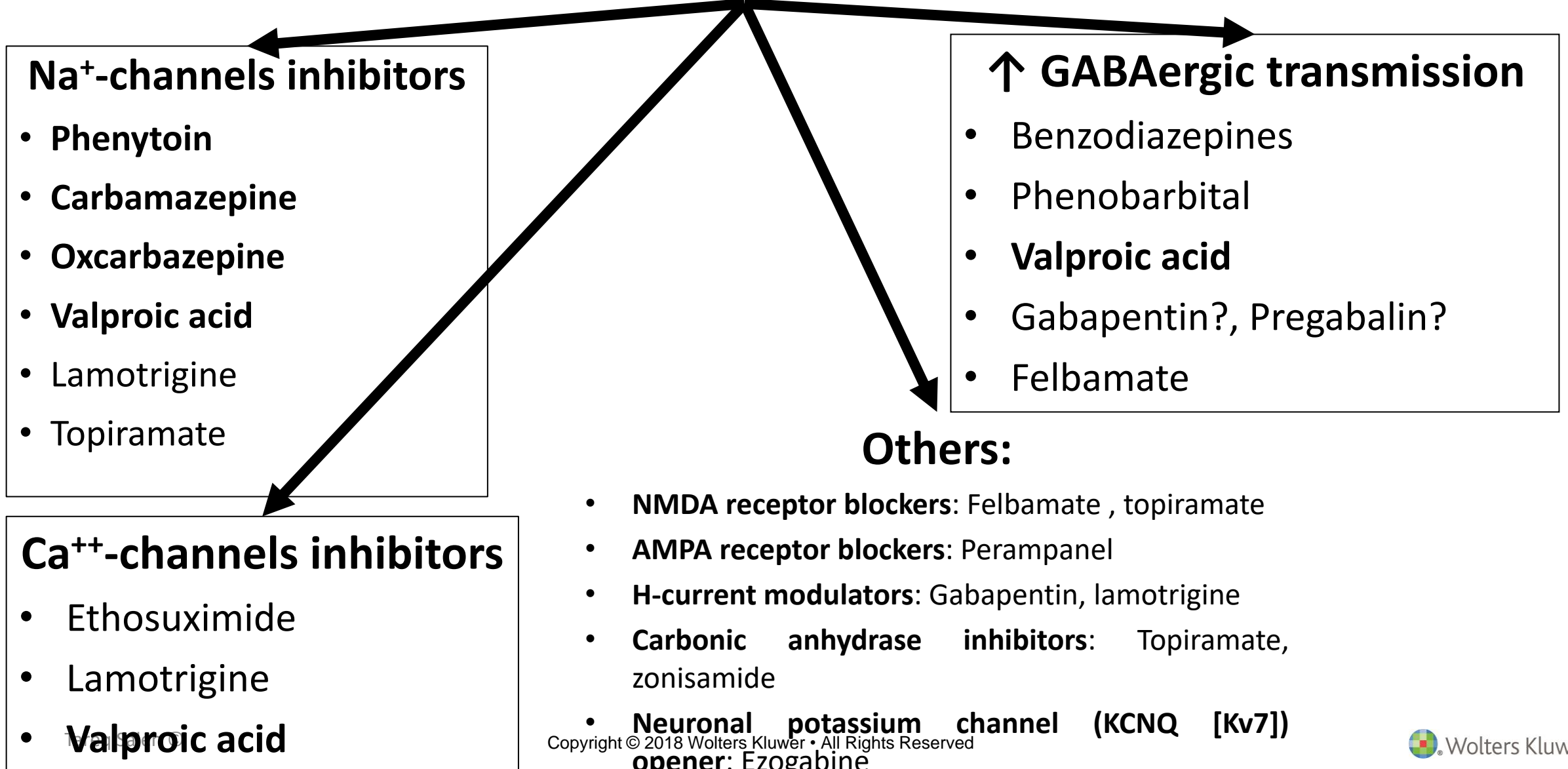
vs

Sodium valproate

vs

Divalproex sodium

Antiepileptic drugs



Lamotrigine

MOA:

- Blocks Na⁺ channels
- Blocks voltage-gated Ca⁺⁺ channels

Indications:

- Focal seizures
- Generalized seizures
- Absence
- Lennox-Gastaut syndrome
- Bipolar disorder

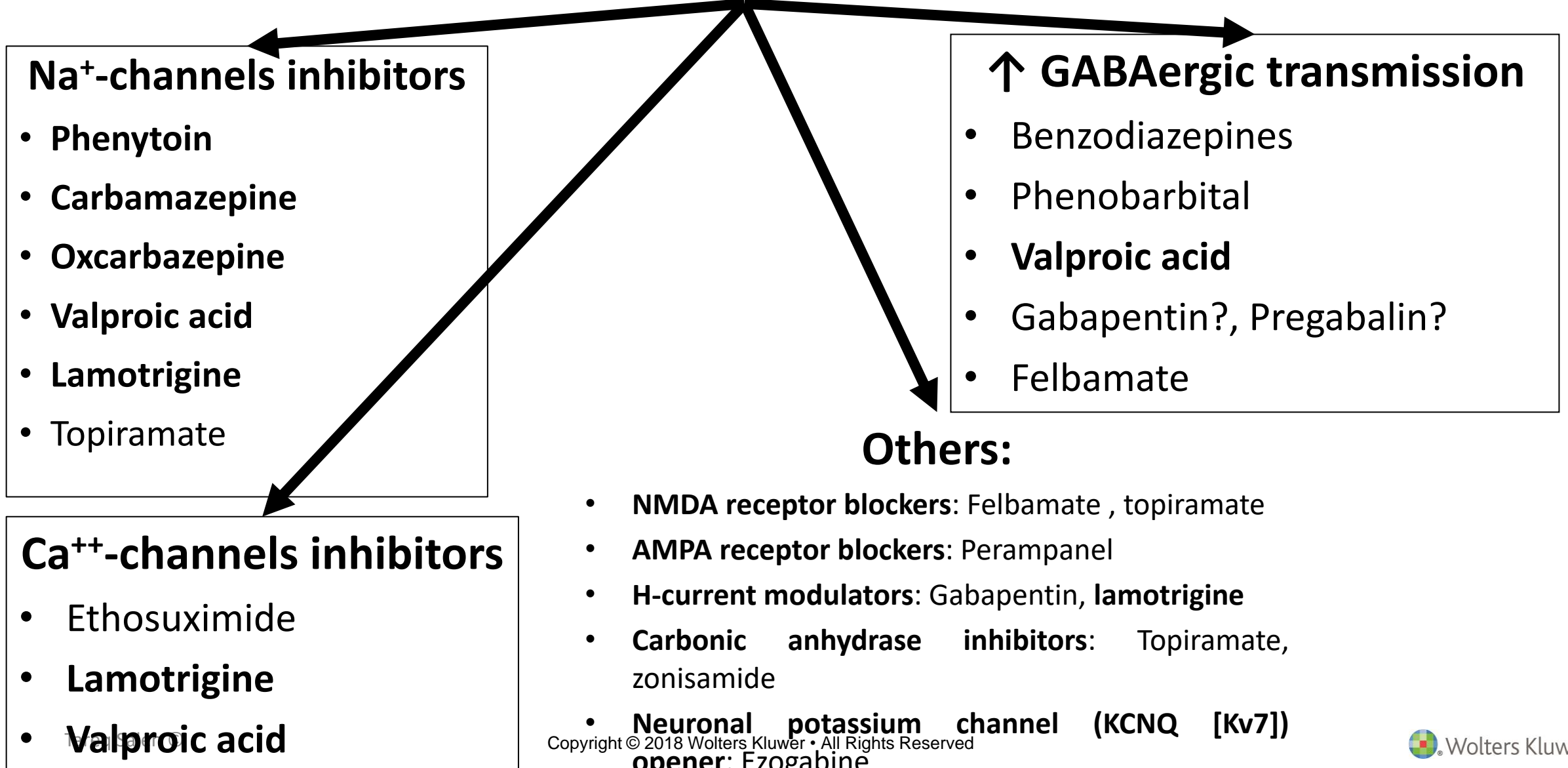
Adverse effects

- CNS-related side effects
- Severe skin reaction (**life-threatening**)

Pharmacokinetics:

- Metabolized by UGT
- What will happen when combined with *phenytoin*?
Valproic acid?

Antiepileptic drugs



Topiramate

MOA:

- Blocks Na⁺ channels
- Blocks L-type Calcium channels
- Carbonic anhydrase inhibitor
- NMDA blocker

Indications:

- Focal seizures
- Generalized seizures
- Migraine prevention

Pharmacokinetics:

- **Inhibits** CYP2C9

Adverse effects

- Somnolence
- Weight loss
- Paresthesia
- Renal stones
- Oligohidrosis
- hyperthermia

Zonisamide

MOA:

- Blocks Na⁺ channels
- Blocks T-type Calcium channels
- Limited carbonic anhydrase inhibitor

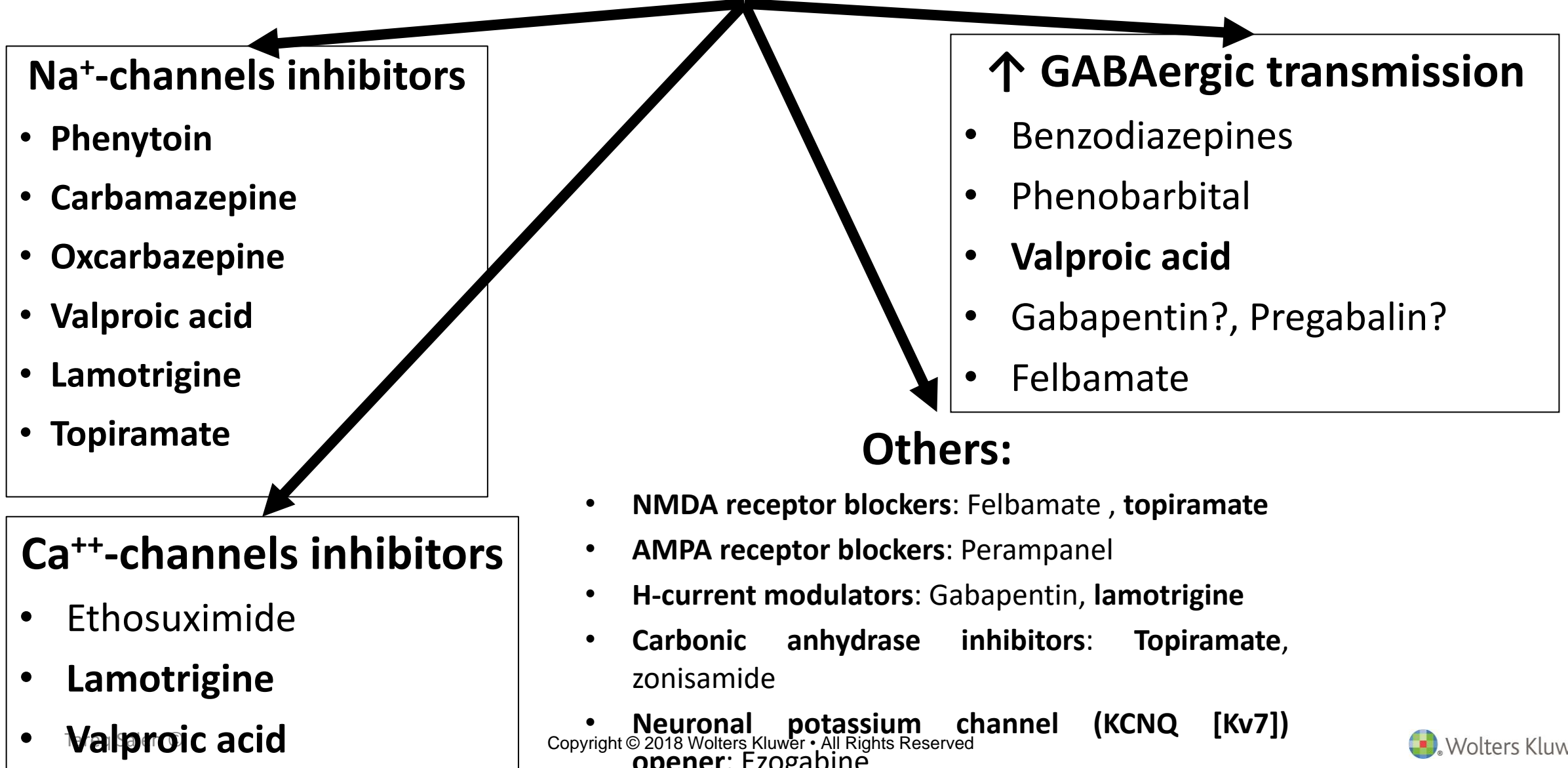
Indications:

- Focal seizures

Adverse effects

- CNS adverse effects
- Nephrolithiasis
- Oligohidrosis
- Contraindicated in patients with sulfonamide hypersensitivity

Antiepileptic drugs



Ethosuximide

MOA:

- Blocks T-type Calcium channels

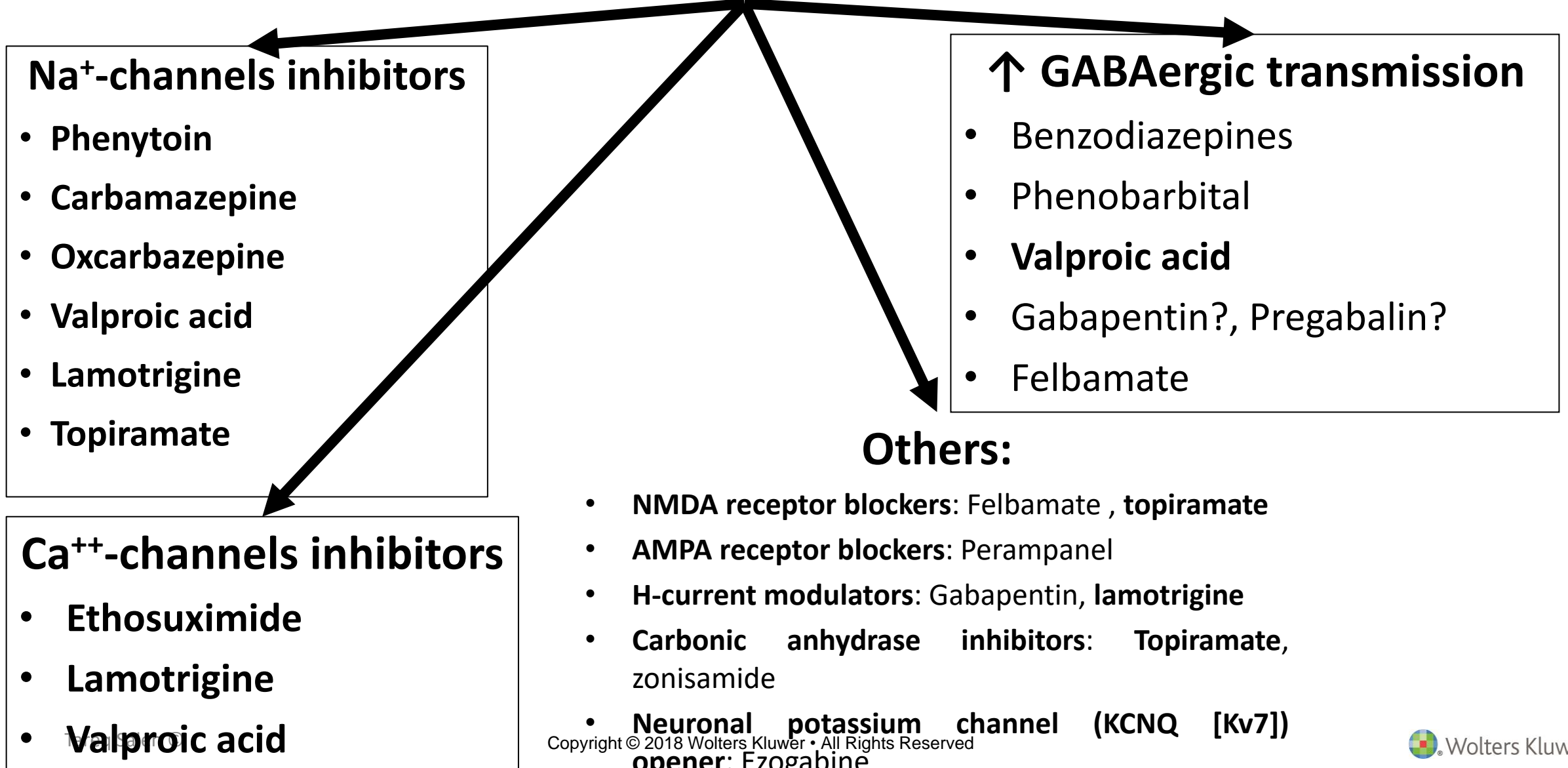
Indications:

- Absence seizure only
(Drug of choice)

Pharmacokinetics:

- Half-life: 30-60 hrs

Antiepileptic drugs





Benzodiazepines Phenobarbital

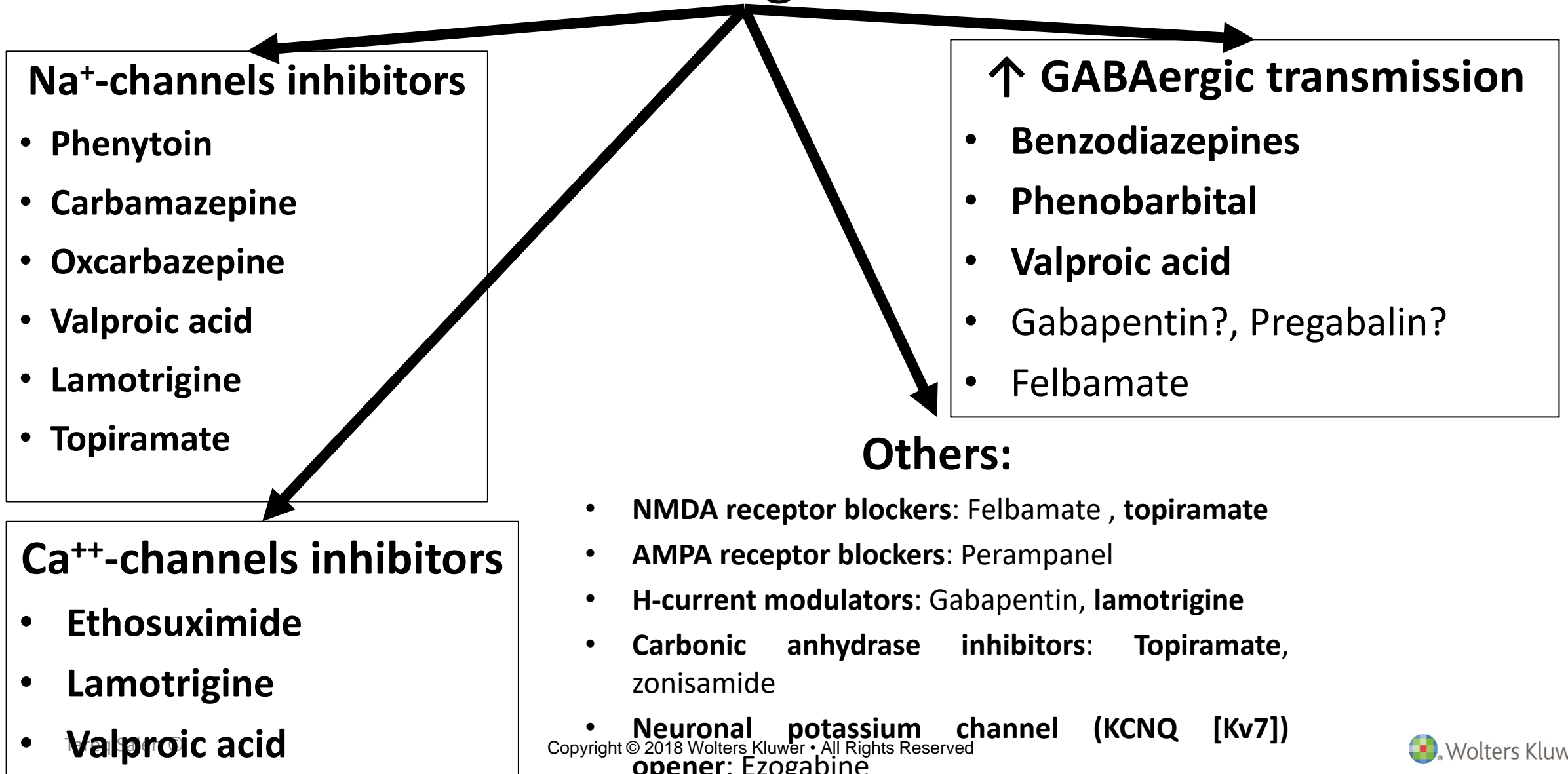
MOA:

- Bind to GABA_A receptors and enhance GABA binding → facilitates Cl⁻ entry → inhibitory

Indications:

- *Clonazepam* → adjunctive antiseizure therapy
- *Diazepam* → status epilepticus (**drug of choice**)

Antiepileptic drugs



Gabapentin Pregabalin

MOA:

- Analog of GABA
- It does **NOT** act at GABA receptor
- MOA is unknown

Adverse effects

- Sedation
- Euphoria

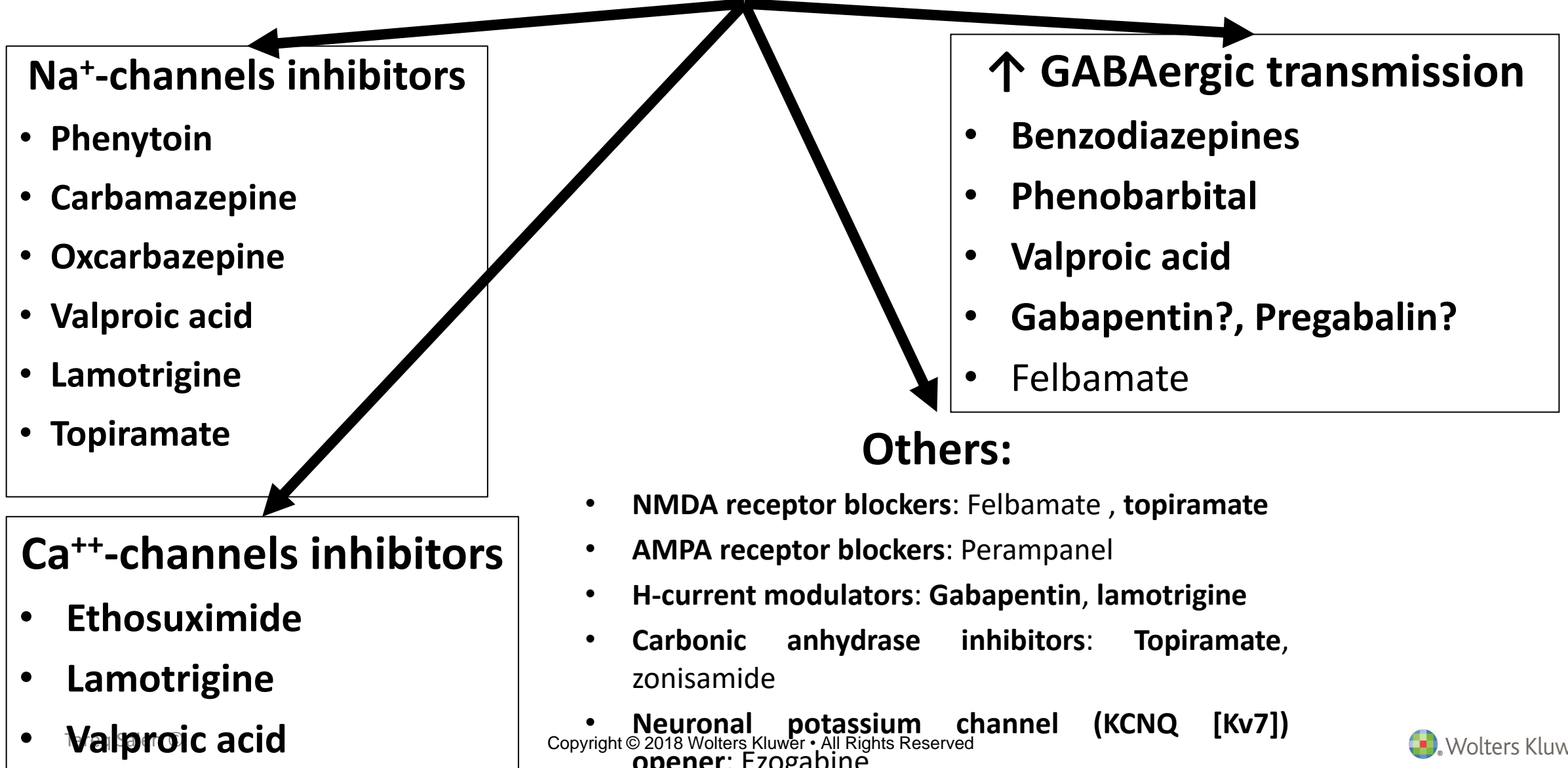
Indications:

- Adjunct therapy for focal seizures
- Neuropathic pain, e.g., postherpetic neuralgia, diabetic neuropathy

Pharmacokinetics:

- Secreted unchanged
- Few drug interactions
- Suitable for elderly

Antiepileptic drugs



Felbamate

MOA:

- Blocks voltage-gated Na⁺ channels
- Blocks NMDA receptors
- Blocks Ca⁺⁺ channels
- Potentiates GABA

Adverse effects

- Aplastic anemia
- Hepatic failure
- Dangerous drug

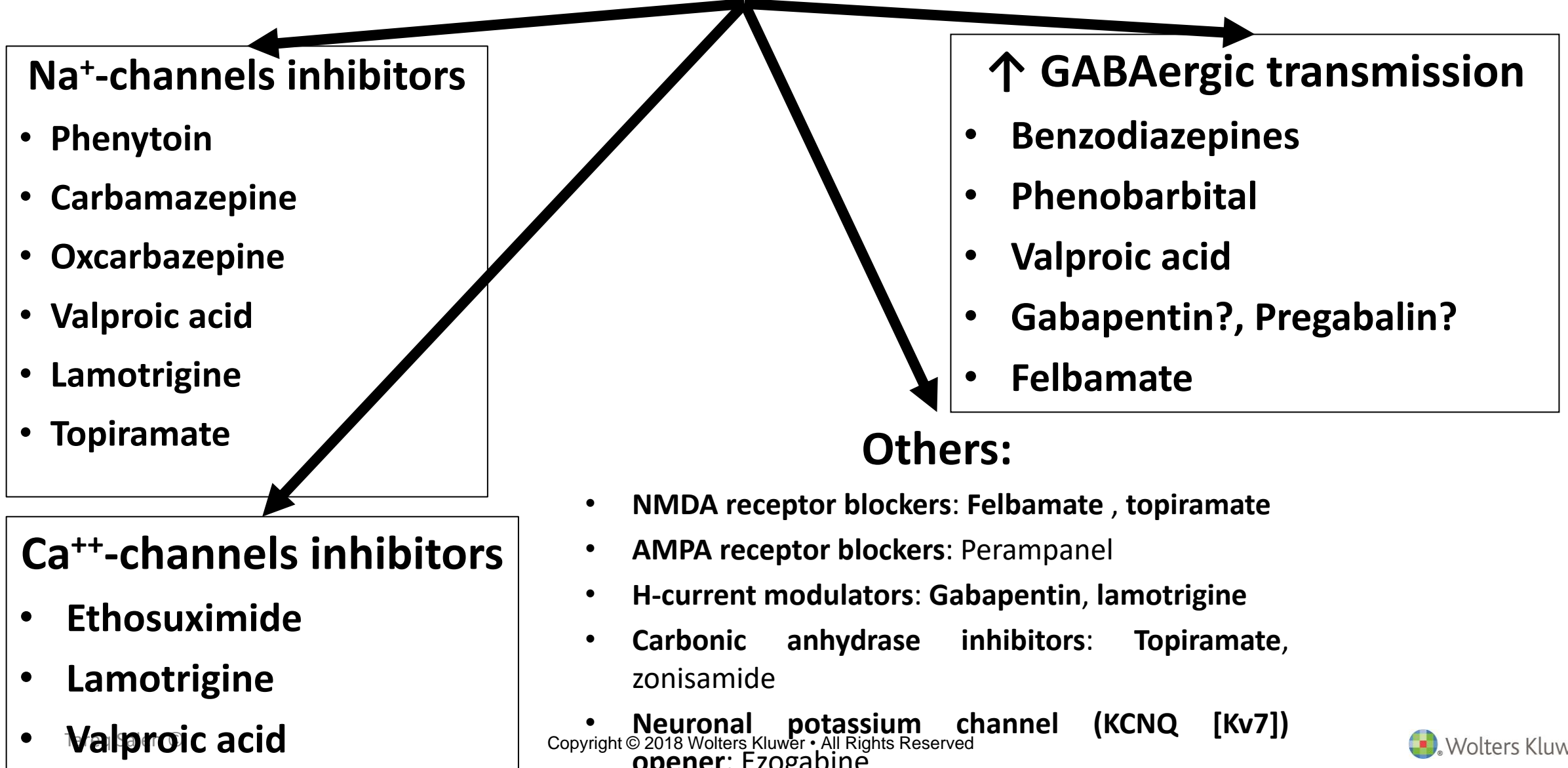
Indications:

- Reserved for refractory epilepsy
- Lennox-Gastaut syndrome

Pharmacokinetics:

- **Inhibits** CYP2C19
- **Induces** CYP3A4

Antiepileptic drugs



Ezogabine

MOA:

- Open voltage-gated M-type potassium channels → stabilizing resting membrane potential

Adverse effects

- Urinary retention
- QT interval prolongation
- Blue skin discoloration
- Retinal abnormalities

Pharmacokinetics:

- No drug interactions at low doses

Levetiracetam

MOA:

- unknown

Indications:

- Focal (simple and complex) seizures
- Adjunct therapy for generalized seizures

Adverse effects

- Dizziness
- somnolence

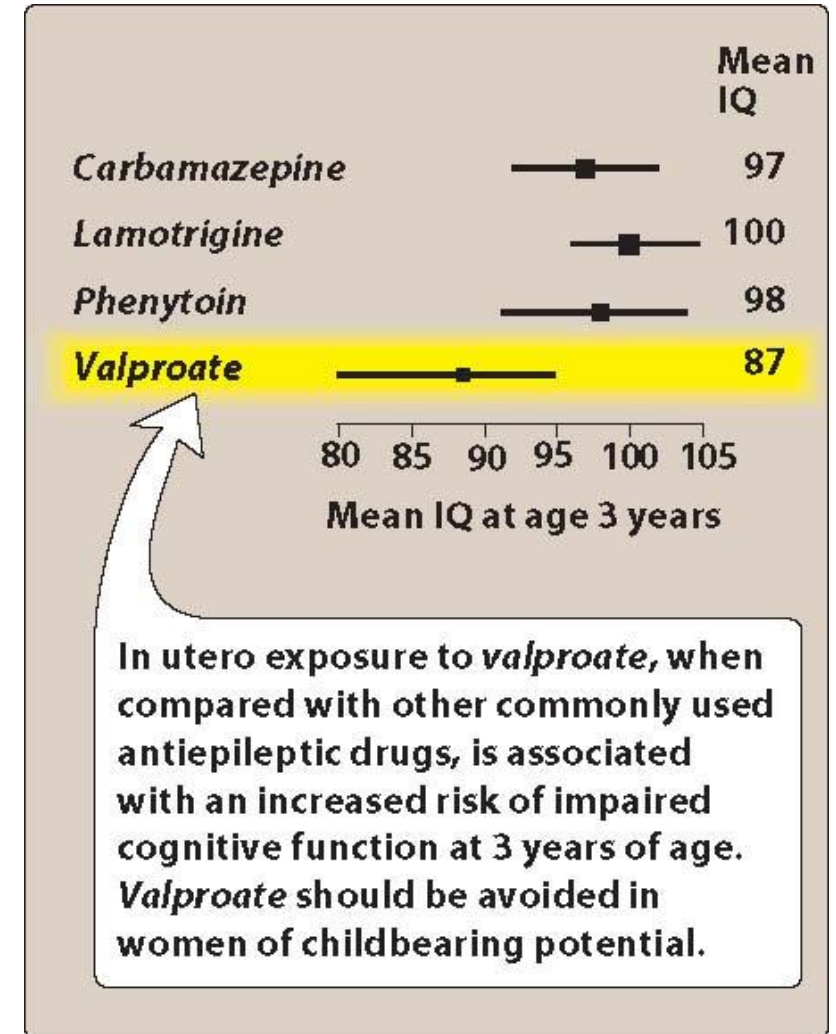


Status Epilepticus

- *Continuous or repetitive seizures (> 20 min) with impaired consciousness during the interictal period.*
- **Management**
 1. **Diazepam** (IV or rectal) → for rapid control.
 2. **Fosphenytoin** (prodrug) or **phenytoin** → long-acting, to maintain control.
 3. **Phenobarbital** → 2nd choice to phenytoin.
 4. **Propofol** (IV anesthesia) → in resistant cases.

Antiepileptics during pregnancy

- Monotherapy
- The lowest possible dose
- Lamotrigine; gabapentin = **safe**
- Valproic acid; phenobarbital; phenytoin, others = **contraindicated**
- *Cleft lip, neural tube defect* (patients considering pregnancy while on antiepileptics should receive folic acid supplements)



Summary of Therapeutic Strategy

Proper diagnosis

Termination of therapy:

- After 2 years (no fits)
- Gradually

Monotherapy

Start with *a small dose* and a **single drug** then gradually increase the dose

Consider monitoring of serum drug levels

Pregnancy:

- Least effective dose of least teratogenic drug
- Folic acid supplements

AAN Guidelines for Epilepsy Treatment



Level	Recommendation
Level B	LTG use should be considered to decrease seizure frequency.
Levels B and Level C	LTG use should be considered (Level B) and GBP use may be considered (Level C) to decrease seizure frequency in patients aged ≥ 60 years.
Level C	LEV use may be considered to decrease seizure frequency.
Level C	ZNS use may be considered to decrease seizure frequency.
Level C	VGB use appears to be less efficacious than immediate-release carbamazepine (CBZ) use and may not be offered; furthermore, toxicity profile precludes VGB use as first-line therapy.
Level C	PGB use at 150 mg/d is possibly less efficacious than LTG use at 100 mg/d.
Level U	Evidence is insufficient to consider GBP, OXC, or TPM instead of CBZ.
Level U	Evidence is insufficient to consider TPM instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic (GTC) seizures, or generalized epilepsy (GE) presenting with GTC seizures.
Level U	Data are lacking to support or refute use of third-generation AEDs, CLB, FBM, or VGB in treating new-onset epilepsy.
Level U	Data are lacking to support or refute use of newer AEDs in treating unclassified GTC seizures.

Recommendation for childhood absence epilepsy

Level	Recommendation
Level B	Unless there are compelling reasons based on adverse events (AEs) profile, ethosuximide (ETS) or VPA use should be considered before LTG use to decrease seizure frequency in treating absence seizures in childhood absence epilepsy.

Figure 12.4 in chapter 12 is
very important



DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
<i>Carbamazepine</i>	Blocks Na ⁺ channels	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
<i>Divalproex</i>	Multiple mechanisms of action	Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.
<i>Eslicarbazepine acetate</i>	Blocks Na ⁺ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
<i>Ethosuximide</i>	Blocks Ca ²⁺ channels	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures.
<i>Ezogabine</i>	Enhances K ⁺ channels	Urinary retention, neuropsychiatric symptoms, dizziness, somnolence, QT prolongation, reports of blue skin discoloration, and retina changes.
<i>Felbamate</i>	Multiple mechanisms of action	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
<i>Gabapentin</i>	Unknown	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination.
<i>Lacosamide</i>	Multiple mechanisms of action	Dizziness, fatigue, and headache. Few drug interactions; Schedule V.
<i>Lamotrigine</i>	Multiple mechanisms of action	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life threatening). Broad spectrum of antiseizure activity.
<i>Levetiracetam</i>	Multiple mechanisms of action	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
<i>Oxcarbazepine</i>	Blocks Na ⁺ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
<i>Perampanel</i>	Blocks AMPA glutamate receptors	Serious psychiatric and behavioral reactions, dizziness, somnolence, fatigue, gait disturbance, and falls, long half-life.
<i>Phenytoin</i>	Blocks Na ⁺ channels	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (<i>fosphenytoin</i>).
<i>Pregabalin</i>	Multiple mechanisms of action	Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination.
<i>Rufinamide</i>	Unknown	Shortened QT interval. Multiple drug interactions.
<i>Tiagabine</i>	Blocks GABA uptake	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
<i>Topiramate</i>	Multiple mechanisms of action	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
<i>Vigabatrin</i>	Irreversible binding of GABA-T	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.
<i>Zonisamide</i>	Multiple mechanisms of action	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.



ANTIPILEPSY MEDICATION	PROTEIN BINDING*	HALF-LIFE	ACTIVE METABOLITE	MAJOR ORGAN OF ELIMINATION	DRUG INTERACTIONS
<i>Carbamazepine</i>	Moderate	6–15	CBZ-10,11-epoxide	Liver	✓
<i>Eslicarbazepine acetate</i> **^	Low	8–24	Eslicarbazepine (S-lcarbazepine)	Kidney	✓
<i>Ethosuximide</i>	Low	25–26		Liver	✓
<i>Ezogabine</i>	Moderate	7–11	monoacetylated metabolite	Liver	✓
<i>Felbamate</i>	Low	20–23		Kidney/Liver	✓
<i>Fosphenytoin</i> **	High	12–60	phenytoin	Liver	✓
<i>Gabapentin</i>	Low	5–9		Kidney	
<i>Lacosamide</i>	Low	13		Various	
<i>Lamotrigine</i>	Low	25–32		Liver	✓
<i>Levetiracetam</i>	Low	6–8		Hydrolysis	
<i>Oxcarbazepine</i> **	Low	5–13	Monohydroxy metabolite (MHD)	Liver	✓
<i>Phenobarbital</i>	Low	72–124		Liver	✓
<i>Phenytoin</i>	High	12–60		Liver	✓
<i>Primidone</i>	High	72–124	Phenobarbital, PEMA	Liver	✓
<i>Perampanel</i> ^	High	105		Liver	✓
<i>Pregabalin</i>	Low	5–6.5		Kidney	
<i>Rufinamide</i>	Low	6–10		Liver	✓
<i>Tiagabine</i>	High	7–9		Liver	✓
<i>Topiramate</i>	Low	21		Various	✓
<i>Vigabatrin</i>	Low	7.5		Kidney	✓
<i>Valproic Acid (Divalproex)</i>	Moderate/High	6–18	Various	Liver	✓
<i>Zonisamide</i>	Low	63		Liver	✓

*Low = 60% or less, Moderate = 61%–85%, High = >85%; ^Newly approved. Limited data in patients available. **Prodrug.