Drugs for Epilepsy (seizures)

overview

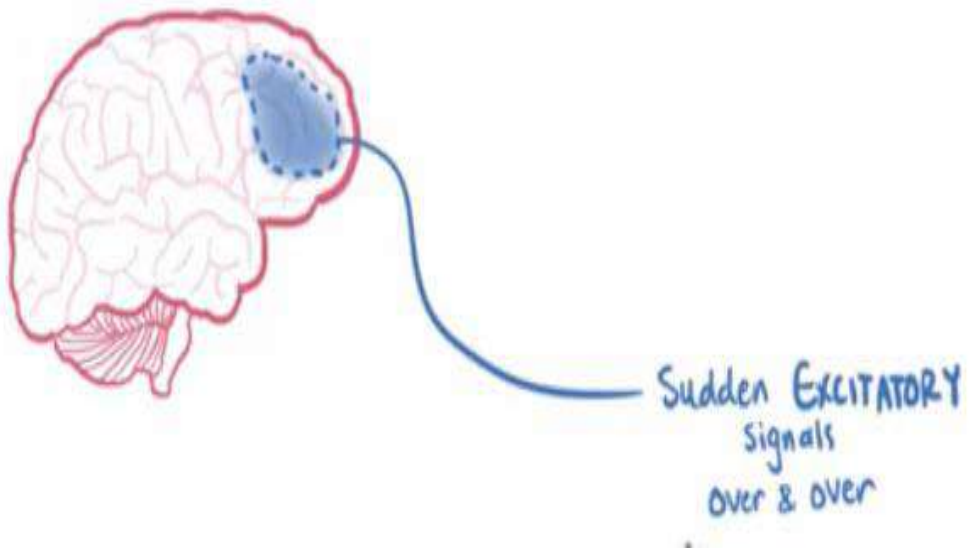
- Epilepsy is the third most common neurologic disorder after cerebrovascular and Alzheimer's disease
- Epilepsy is not one diseases → different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons
- Different range of signs and symptoms come with seizures

overview

- Loss of consciousness, abnormal movements or a generalized convulsion
- visual, auditory, and olfactory hallucinations

- Seizures can be controlled with one medication in approximately 75% of patients
- Anti-epilepsy medications are needed if the primary cause is not corrected or not known

Etiology and classification

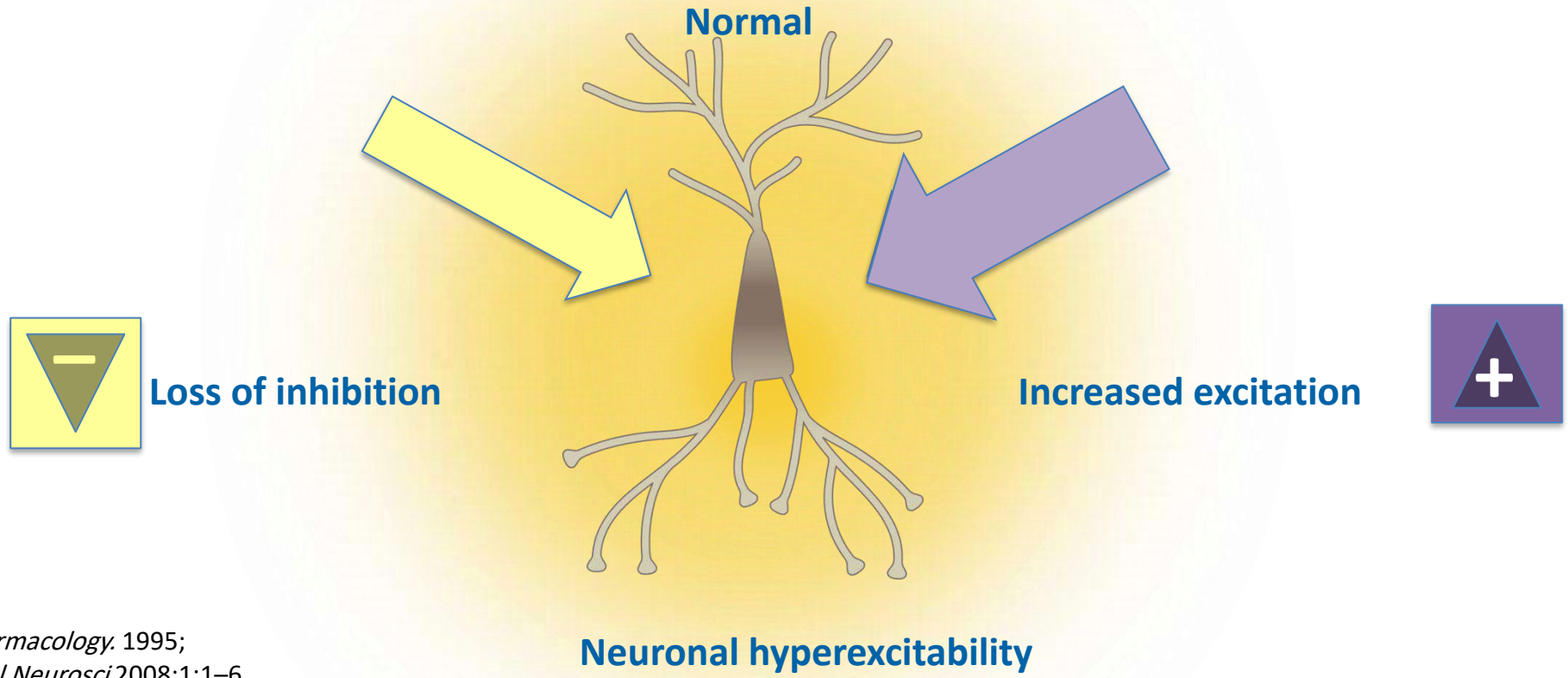


Violent firing of action potential

- Seizure: abrupt\transient signs and symptoms due to abnormal neurons activity (paroxysmal (violent firing) electrical discharge)

- Not every seizure is convulsive
- Convulsion: mainly motor seizure → involuntary movement *Convulsive seizure (abnormal neuronal firing involving the motor cortex)
- Usually generalized (all the brain is involved)
- Partial seizures (part of the brain) with different manifestations (phenomena)

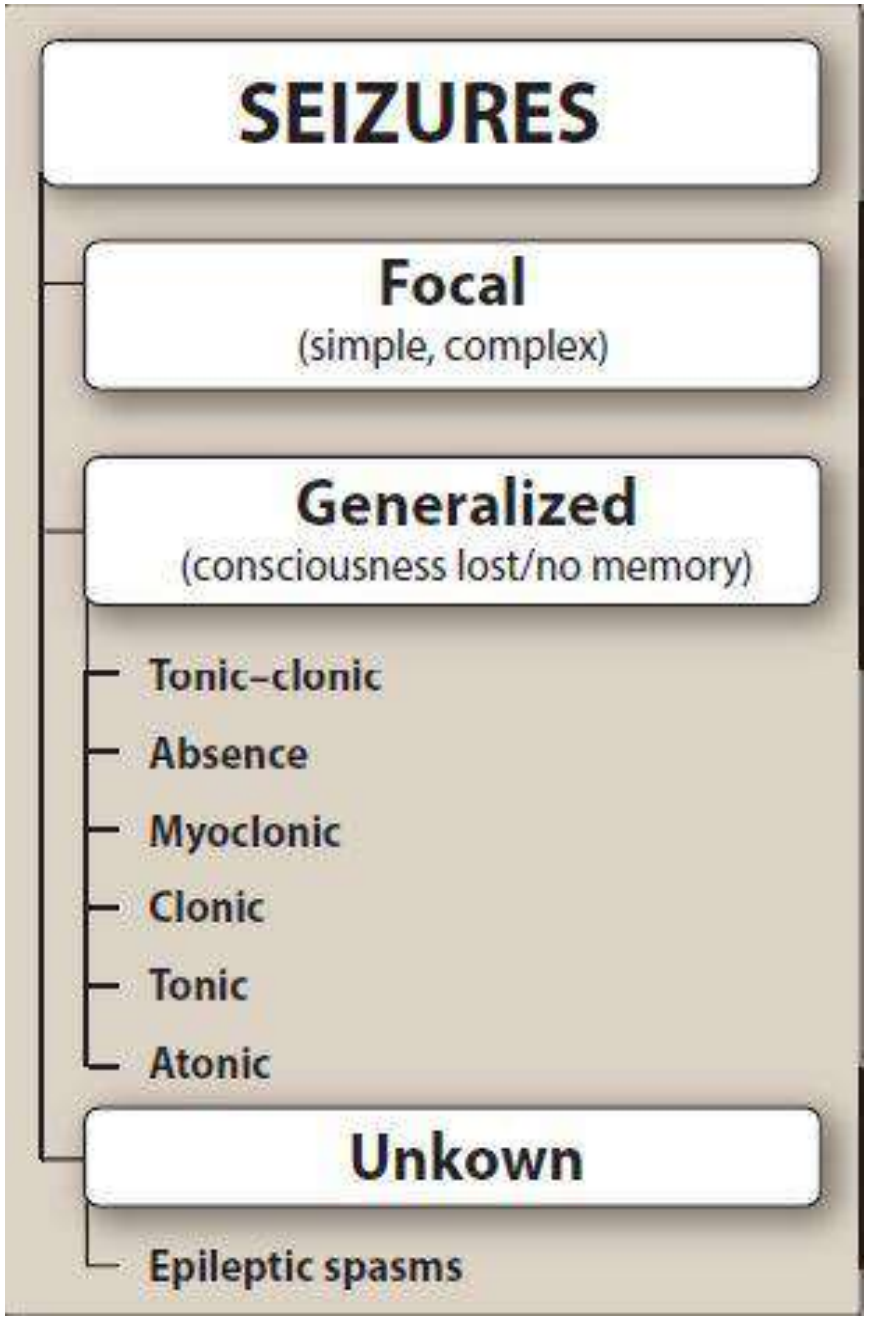
- Normally, inhibitory and excitatory systems in the brain are balanced
- When this normal balance is disrupted, neurons can become hyperexcitable (abnormal electrical activity)
  - Loss of inhibition
  - Increased excitation



Rang HP *et al. In: Pharmacology.* 1995;
Fritschy JM. *Front Mol Neurosci* 2008;1:1–6.

Classification of epileptic seizures:

- Focal → portion of the brain is involved
- Generalized (6 types) → both hemispheres of the brain
- **Tonic**: continuous contraction
- **Clonic**: rapid repeated contraction and relaxation happening in bilateral rhythmic way
- Myoclonic: consist of short episodes of muscle contractions
- Atonic → drop attacks



Mechanism of action of anti-epilepsy medications

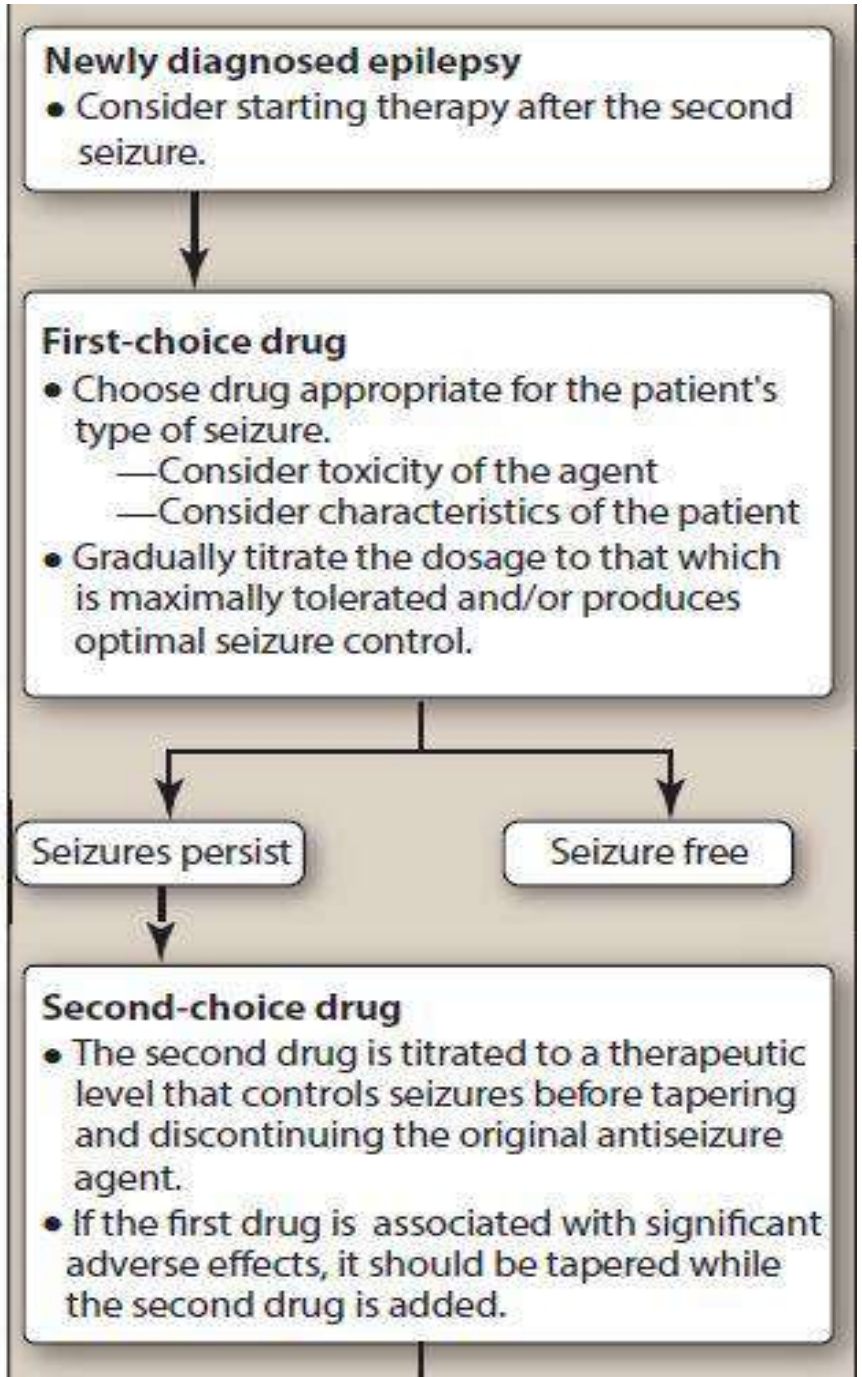
- Blocking voltage-gated channels (Na+ or Ca2+)
- Enhancing inhibitory (GABA)-ergic impulses
- interfering with excitatory glutamate transmission
- Some anti-epilepsy medications appear to have multiple targets within the CNS
- Anti-epilepsy medications suppress seizures but do not “cure” or “prevent” epilepsy

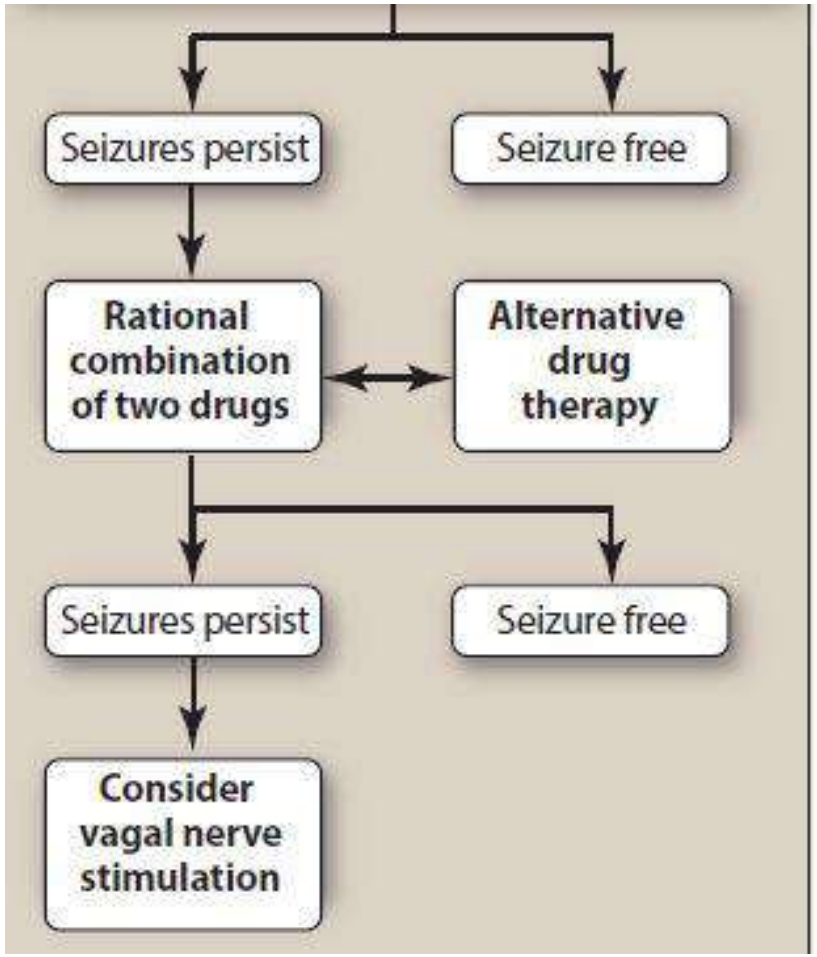
Drug selection

- Efficacy is comparable
- Type of seizure, toxicity of agent and ch.ch of patient help in the choice (age, comorbid medical conditions, lifestyle, and personal preference)
- Monotherapy is recommended → patients receiving monotherapy exhibit better medication adherence and fewer side effects
- monotherapy with an alternate medication or the addition of medications should be considered

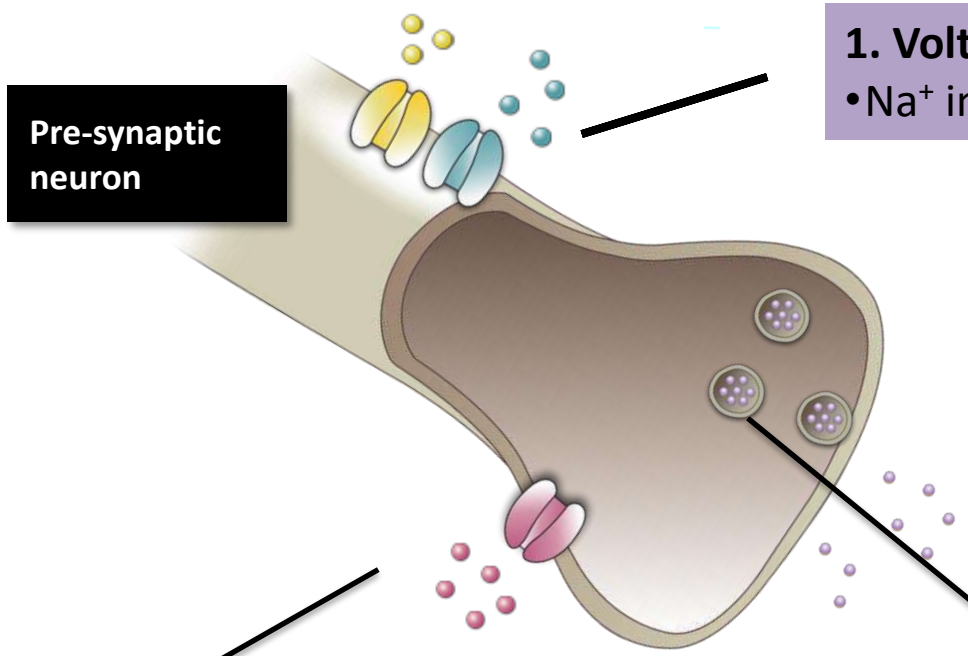
- **Other considerations**
- P.K predictability Interactions – some newer agents have no interactions (cytochrome enzymes induction or inhibition) → Levetiracetam \ Gabapentin \ pregabalin

Drug selection





Mechanism of action of anti-epilepsy medications



1. Voltage-gated Na^+ channel[1,2]
- Na^+ influx increases excitability and drives action potentials

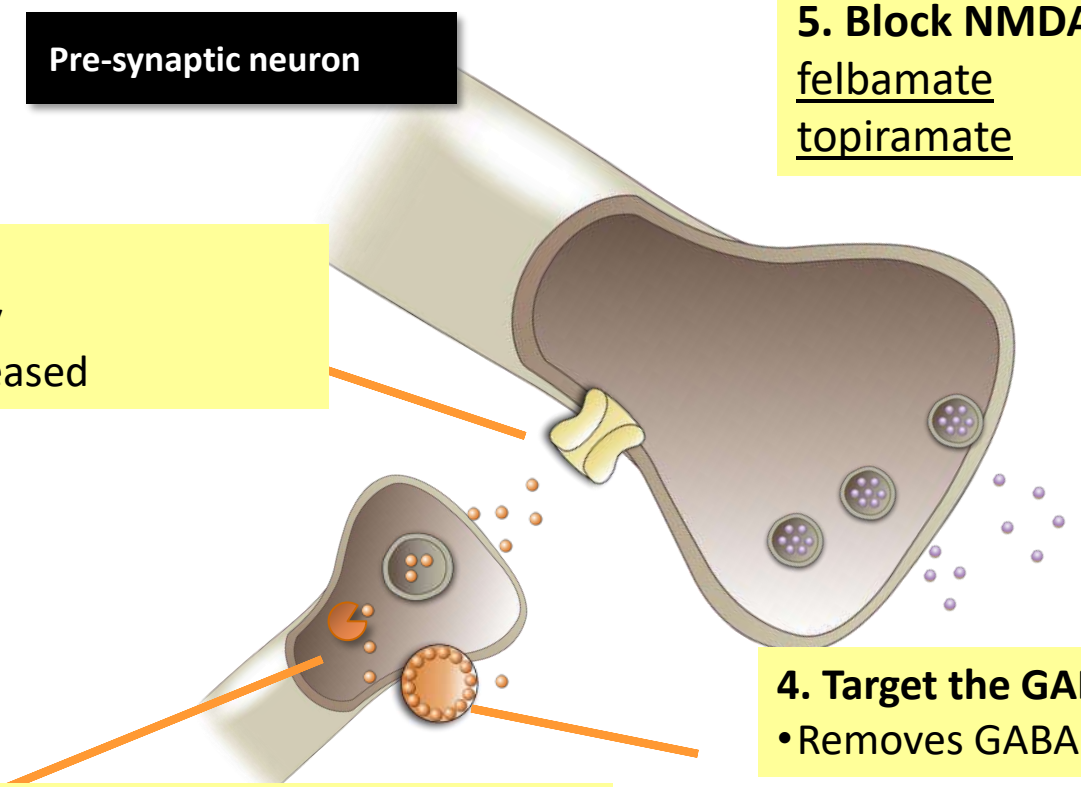
Neurotransmitter release

3. Synaptic vesicle protein 2A (SV2A)[1,2]
- Required for release of neurotransmitter from vesicles

2. Voltage-gated Ca^{2+} channel[1,2]
- Ca^{2+} influx drives neurotransmitter release

Redrawn and adapted from [1]
[1]Rogawski MA, Löscher W. *Nat Rev Neurosci* 2004;5:553–564; [2]Brodie MJ. *Seizure* 2010;19:650–655; [3]Trobalt. Summary of product characteristics, 2011; [4]Potiga. Prescribing information, 2011.

Mechanism of action of anti-epilepsy medications



5. Block NMDA glutamate receptors
felbamate
topiramate

4. Target the $GABA_A$ receptor
- Reduces neuronal excitability
- $GABA_A$ receptor activity increased

4. Target the GABA transporter
- Removes GABA from the synapse

4. Target GABA transaminase
- Degrades GABA

Rogawski MA, Löscher W. *Nat Rev Neurosci* 2004;5:553–564; Brodie MJ. *Seizure* 2010;19:650–655.

Anti-epilepsy medications

FDA approved many new anti-epilepsy medications

potential advantages of newer agents regarding pharmacokinetics, tolerability, and reduced risk for drug–drug interactions.

studies have failed to demonstrate that the newer drugs are significantly more efficacious than the older agents.

Most anti-epilepsy medications are associated with hypersensitivity

APPROVED AFTER 1990

- *Clobazam* ONFI
- *Eslicarbazepine* APTIOM
- *Ezogabine* POTIGA
- *Felbamate* FELBATOL
- *Fosphenytoin* CEREBYX
- *Gabapentin* NEURONTIN
- *Lacosamide* VIMPAT
- *Lamotrigine* LAMICTAL
- *Levetiracetam* KEPPRA
- *Oxcarbazepine* TRILEPTAL
- *Perampanel* FYCOMPA
- *Pregabalin* LYRICA
- *Rufinamide* BANZEL
- *Tiagabine* GABITRIL
- *Topiramate* TOPAMAX
- *Vigabatrin* SABRIL
- *Zonisamide* ZONEGRAN

APPROVED BEFORE 1990

- *Carbamazepine* TEGRETOL
- *Diazepam* VALIUM
- *Divalproex* DEPAKOTE
- *Ethosuximide* ZARONTIN
- *Lorazepam* ATIVAN
- *Phenobarbital* LUMINAL
- *Phenytoin* DILANTIN
- *Primidone* MYSOLINE

Benzodiazepines

- Diazepam and lorazepam are usually reserved for emergency or acute seizure treatment due to tolerance (in prolonged tonic-clonic)
- Clonazepam and Clobazam may be prescribed as adjunctive therapy for particular types of seizures.
- Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate.
- Always used in emergency statues epilepticus → diazepam

Carbamazepine

- **MAO**: blocks sodium voltage gated channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread.
- effective for treatment of **focal** seizures, **generalized tonic–clonic** seizures, neuralgia, and bipolar disorder.
- Potent enzyme inducer
- At higher doses → It induces its own metabolism, resulting in lower total carbamazepine blood concentrations.

Carbamazepine

- Carbamazepine is an inducer of many CYP enzymes which increases the clearance of other drugs
- **Adverse effect**: Hyponatremia (elderly)
- Contraindicated in absence seizures because it may cause an increase in seizures

Ethosuximide:

- Voltage-gated Ca2+ channel → Ca2+ influx drives neurotransmitter release
- Inhibits T-type calcium channels
- It is only effective in treating **absence seizures**

Felbamate

- has a broad spectrum of anticonvulsant action with multiple proposed mechanisms:
- Blocking of voltage-dependent sodium channels
- competing with the glycine co-agonist binding site on the N-methyl-d-aspartate (NMDA) glutamate receptor
- blocking of calcium channels
- potentiating GABA action
- Affects cytochrome enzymes
- reserved for use in **refractory epilepsies**
- Aplastic anemia and hepatic failure

Gabapentin

- **Gabapentin** is approved as adjunct therapy for focal seizures and treatment of post-herpetic neuralgia (neuropathic pain)
- GABA analogue but does not affect GABA actions or work on its receptors
- Mechanism of action is not known
- Good choice for the elderly with partial seizures (mild adverse effects)

Lamotrigine

- It blocks sodium channels, as well as high voltage-dependent calcium channels
- Effective in a wide variety of seizure types, including focal, generalized and absence seizures (bipolar disorder)
- Enzyme inducers like **phenobarbital and carbamazepine** lead to lower lamotrigine concentrations (loss of efficacy)
- **Valproate** will inhibit lamotrigine's metabolism → higher lamotrigine concentrations
- Dose adjustment and slow titration is required
- Slow titration is necessary with lamotrigine (particularly when adding lamotrigine to a regimen that includes valproate) due to risk of rash, which may progress to a serious, life-threatening reaction.

levetiracetam

- Synaptic vesicle protein 2A (SV2A) → Required for release of neurotransmitter from vesicles → inhibited by levetiracetam
- Still MOA is not clearly understood
- Approved for adjunct therapy of focal onset, myoclonic, and primary generalized tonic–clonic seizures in adults and children
- No drug interaction
- it can cause mood alterations that may require a dose reduction or a change of medication.

Phenobarbital and Primidone (prodrug):

- Primidone is metabolized majorly to phenobarbital
- MOA→ enhancement of the inhibitory effects of GABA-mediated neurons → reducing neuronal excitability
- Phenobarbital is used primarily in the treatment of status epilepticus when other agents fail

Phenytoin and Fosphenytoin (prodrug)

- Fosphenytoin is a prodrug rapidly converted to **phenytoin** in the blood within minutes. It can be administered intramuscularly (IM), phenytoin sodium should never be given IM, as it causes tissue damage and necrosis.
- Fosphenytoin is the drug of choice and standard of care for IV and IM administration of **phenytoin**

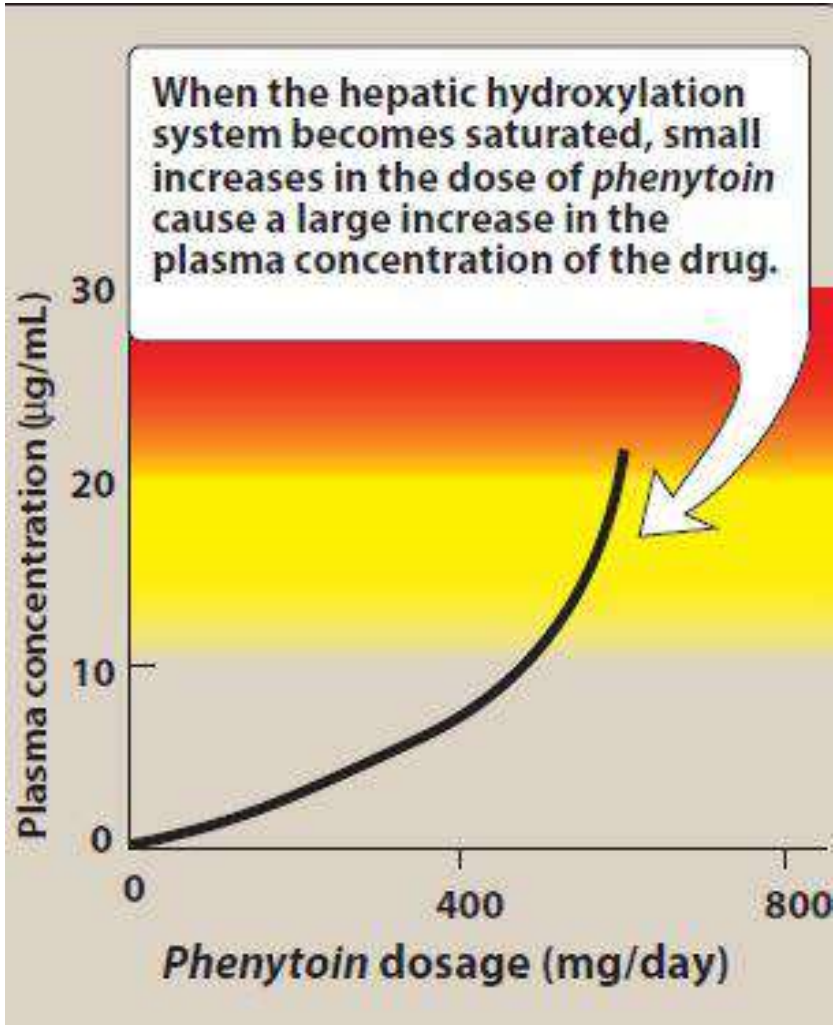
- **MOA**: blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery.
- It is effective for treatment of focal and generalized tonic– clonic seizures and in the treatment of status epilepticus

Phenytoin and Fosphenytoin (prodrug)

- **Low cost but Serious toxicity and adverse effects:**
- Gingival hyperplasia (gum growing over the teeth)
- CNS depression at cerebellum and vestibular system → nystagmus (dancing eyes) and ataxia
- Long-term use may lead to development of peripheral neuropathies and osteoporosis

Phenytoin and Fosphenytoin (prodrug)

- Potent cytochrome enzyme inducer
- It exhibits nonlinear pharmacokinetic properties at higher concentrations
- Exhibits saturable enzyme metabolism
- small increases in the daily dose can produce large increases in plasma concentration



Pregabalin

- **Pregabalin** blocks voltage-gated calcium channels in the CNS (α2-δ site, an auxiliary subunit) , inhibiting excitatory neurotransmitter release
- Indications: Focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia
- Renal elimination (dose adj in renal dysfunction)
- Weight gain and peripheral edema

Drugs targeting GABA neurotransmitter (potentiating CNS inhibition)

- **Tiagabine**
- Inhibits GABA reuptake (inhibits its transporter)
- effective as adjunctive treatment in partial-onset seizures
- causes seizures for epilepsy free patients
- Tiagabine should not be used for indications other than epilepsy

Topiramate

- **MOA's:**
- blocks voltage-dependent sodium channels and high-voltage calcium currents (L type)
- Block NMDA receptors
- effective for use in partial and primary generalized epilepsy.
- It is also approved for prevention of migraine.
- Cytochrome inhibitor and is induced by phenytoin and carbamazepine.
- **Adverse effects:**
- somnolence, weight loss, and paresthesias
- Renal stones, glaucoma, oligohidrosis (decreased sweating), and hyperthermia (rare)

Valproic acid and sodium valproate (divalproex)

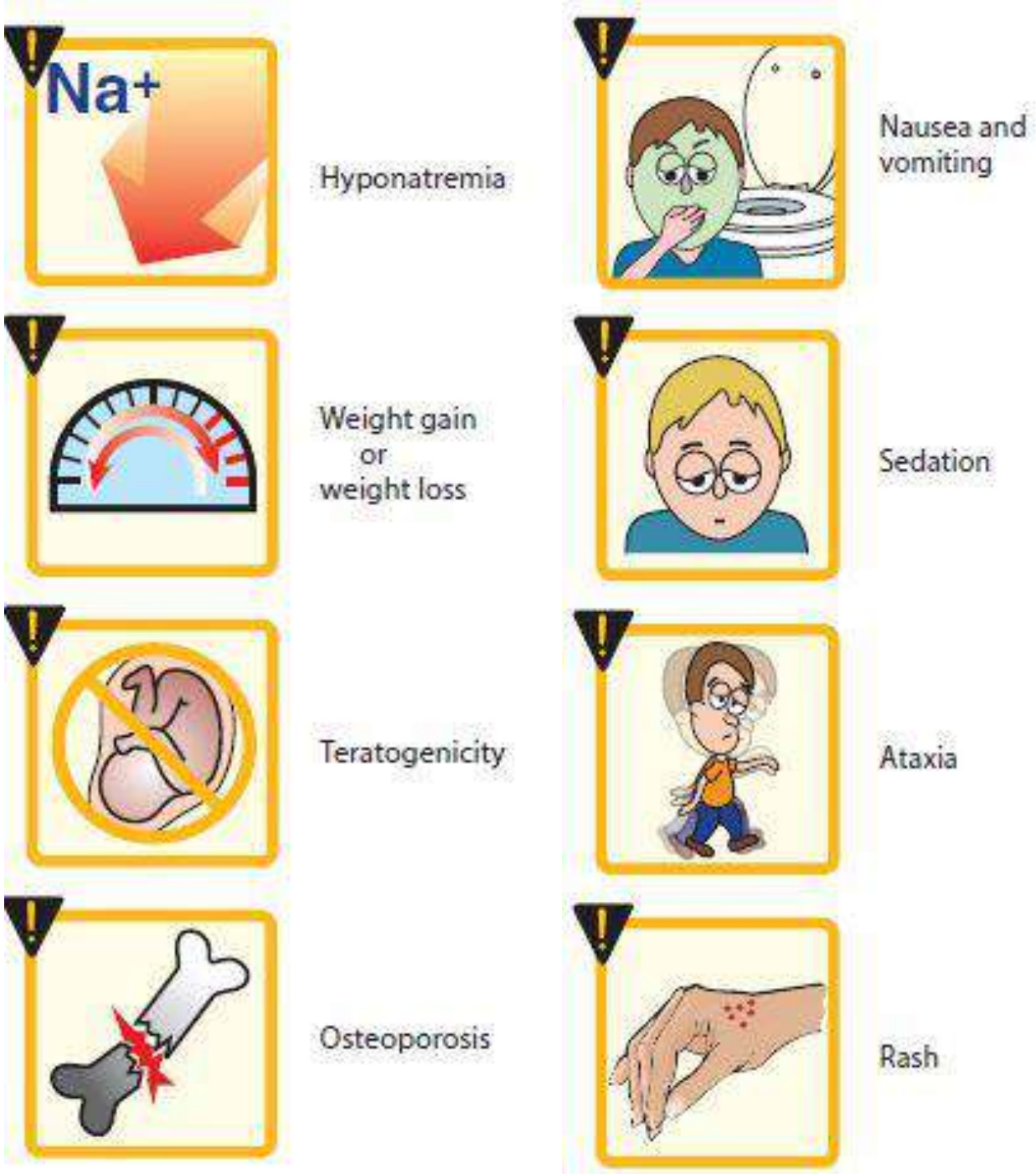
- **Possible MOA's include** sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels (broad effective spectrum)
- It is effective for the treatment of focal and primary generalized epilepsies.
- Valproic acid is available as a free acid
- Sodium valproate → salt formulation (better GI tolerance)
- Combination of sodium valproate and valproic acid (convert to valproate) → Divalproex Na
- Cytochrome enzyme inhibitor
- Teratogenic
- Hepatotoxicity (rare) → LFTs must be monitored frequently

Drugs targeting GABA neurotransmitter (potentiating CNS inhibition)

- **Vigabatrin**
- an irreversible inhibitor of γ-aminobutyric acid transaminase (enzyme responsible for metabolism of GABA)
- It is associated with visual field loss ranging from mild to severe in 30% or more of patients

Common adverse effects

- Suicidal behavior and suicidal ideation → risk with anti-epilepsy medications.
- multiorgan hypersensitivity reactions → a rare idiosyncratic reaction characterized by rash, fever, and systemic organ involvement
- Fig 12.7



Status epilepticus

- Life threatening emergency in which two or more seizures are happening back-to-back
- no recovery of full consciousness between them
- continuous seizure lasting > 5 min
- > 30 min
- Focal or generalized
- Convulsive or non-convulsive
- Diazepam and lorazepam are used for the acute fast management
- followed by a slower acting AED → fosphenytoin (phenytoin) → if seizures persisted: phenobarbital