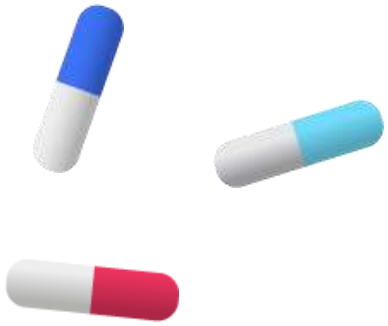
UNIT 3



Key Concepts in Pharmacology

MEDICAL SCHOOL COMPANION

Diuretics: Overview

- Widely used to treat hypertension, congestive heart failure, edema, and electrolyte abnormalities

- Major diuretic classes:
  - Osmotic diuretics
  - Carbonic anhydrase inhibitors
  - Loop diuretics
  - Thiazides
  - Potassium-sparing

Osmotic Diuretics: Overview

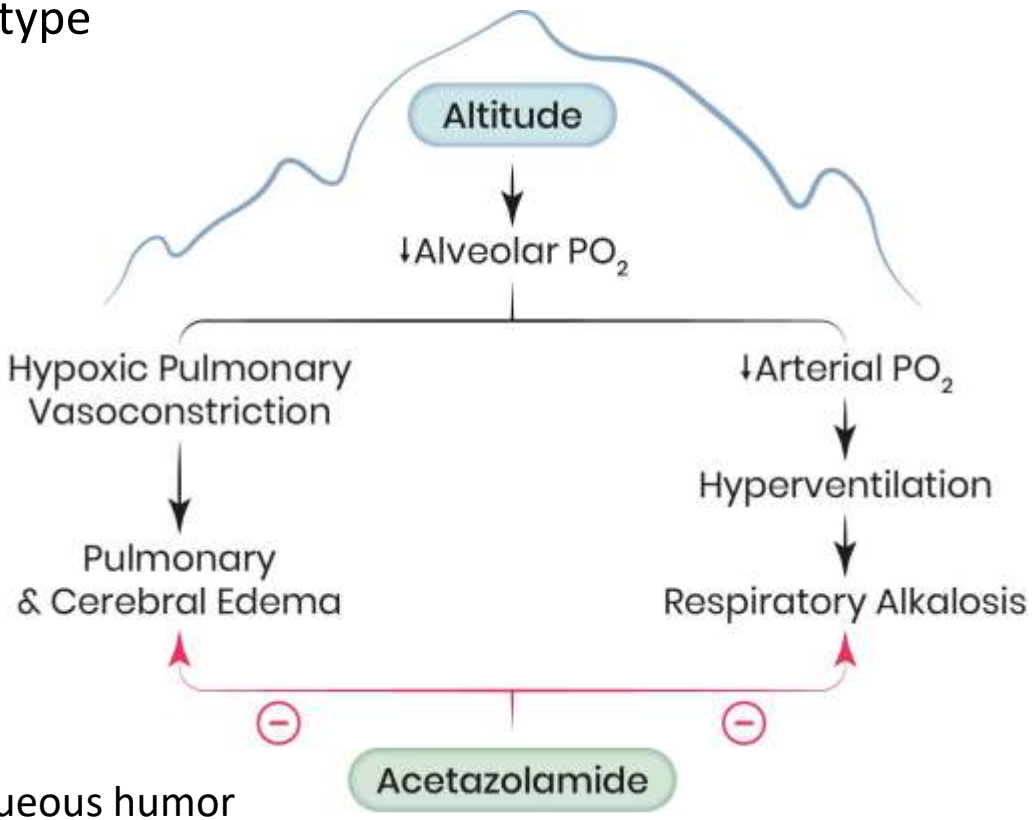
- Include *mannitol*, *glycerin*, and *isosorbide*
- Freely filtered at the glomerulus
- Undergo limited or negligible reabsorption by the renal tubule
- Relatively inert pharmacologically
- Extract water from intracellular compartments and thereby expand extracellular fluid volume
  - Caution when using in patients with pre-existing pulmonary edema, can exacerbate it
- Major clinical uses:
  - Reduce intracranial pressure in cases of cerebral edema
  - Reduce intraocular pressure during acute attacks of glaucoma
  - Preserve urine volume in acute renal failure

Osmotic Diuretics

- **Adverse effects:**
  - Nausea and vomiting
  - Pulmonary edema
    - Can occur if fluid drawn out of tissues overwhelms cardiovascular status
    - Especially in patients with heart failure or marginal renal function

Carbonic Anhydrase Inhibitors

- Inhibit carbonic anhydrase in proximal tubular epithelial cells
  - *Acetazolamide* is the prototype
  - Sulfonamide derivatives
- **Therapeutic uses:**
  - Mountain sickness
    - Induces metabolic acidosis



  - Open-angle glaucoma
    - Decreases formation of aqueous humor
  - Manage edema due to congestive heart failure or drugs
    - Uncommon usage today

Carbonic Anhydrase Inhibitors

- CA inhibition in the PCT lumen causes:
  - Blockade of H_2CO_3 -> $H_20 + CO_2$
  - Increased urinary Na/HCO_3^- loss since H_2CO_3 requires conversion to CO_2 for absorption
  - Inhibited Na^+/H^+ antiporter activity (inability to acidify urine)
- CA inhibition in the PCT luminal cell causes:
  - Blockade of $H_20 + CO_2$ -> HCO_3^- and H^+ in the cytosol
  - Prevents reuptake of HCO_3^- back into the serum
- Urinary Na+/HCO3- are increased (H2O follows)
  - Diuretic Effect
- Urinary H+ and Cl- are decreased
  - Urine alkalosis and plasma acidosis

Carbonic Anhydrase Inhibitors

- **Adverse effects:**
  - Metabolic acidosis
  - Electrolyte disturbances (hypokalemia)
  - Allergic reactions (cross-reactivity with other sulfonamide drug)

Loop Diuretics: Overview

- Inhibit Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending loop of Henle
  - Cause sodium, chloride and potassium loss into the urine
  - Secondarily cause increased excretion of Ca^{2+} and Mg^{2+} due to loss of normal transepithelial voltage from inhibition of the cotransporter.
    - Normally, Mg and Ca are "pulled" by a negative charge on the interstitial side of the cell that is set up by K^+ recycling
    - K^+ recycling is abolished by the loop diuretic
- Powerful diuretics
- Also known to cause vasodilation by increasing prostaglandin production

Loop Diuretics

- **Therapeutic uses:**
  - Acute pulmonary edema
  - Congestive heart failure
  - Acute renal failure
  - Hypercalcemic states

Loop Diuretics

- Furosemide (Lasix®, “lasts six hours”)
- Bumetanide – more potent
- Ethacrynic acid – prototype, safer in patients with sulfa allergies
- Torsemide – better absorbed from the GI tract
- **Adverse effects:**
  - Hypokalemia
    - Danger when used with cardiac glycosides
  - Hyponatremia
  - Volume depletion
  - Hyperuricemia
  - Ototoxicity
    - Especially with IV ethacrynic acid
  - Cross-reacts with sulfa components

Thiazides: Overview

- Inhibit the Na^+/Cl^- cotransporter in the distal convoluted tubule
  - Less efficacious than loop diuretics since 90% of filtered Na^+ reabsorbed prior to DCT
- Increase urinary levels of Na^+, K^+, and Cl^- but decrease levels of Ca^{2+}
  - Cause hypercalcemia

Thiazides:
Overview

- Side effects of thiazides are many, including hyperglycemia, hyperuricemia, hyperlipidemia, hypokalemic alkalosis
- These drugs also have a sulfa component

- **Therapeutic uses:**
  - Hypertension
  - Congestive heart failure
  - Edematous states
  - Calcium-based kidney stone treatment

Thiazides

- Hydrochlorothiazide
- Chlorthalidone
- Metolazone
- Indapamide

Thiazides

- **Adverse effects:**
  - Volume depletion
    - Hypotension
  - Electrolyte disturbances
    - Hypokalemia – usually not as severe as loop diuretics
    - Hyponatremia
    - **Hypercalcemia**
    - Hyperuricemia (exacerbate gout)
    - Metabolic alkalosis

Thiazides

- **Adverse effects:**
  - CNS
    - Headache
    - Paresthesias
  - Sexual
    - Impotence
  - Dermatological disorders
  - Sulfonamide allergies
  - Glucose intolerance (due to thiazide activation of beta-cell K-channels, leading to hyperpolarization) (putative mechanism)

Potassium-Sparing Diuretics

- Spironolactone, amiloride, and triamterene
- Weak diuretics
  - act on distal tubules and collecting ducts
- Rarely employed as single agents
- Offset potassium wasting effects of loop or thiazide diuretics

Amiloride and Triamterene

- Block sodium channels in distal tubules and collecting ducts
  - ENaC channels in principal cells in collecting duct
  - This channel also carries lithium ions
    - Amiloride used in the management of lithium-induced diabetes insipidus
- Adverse effects: metabolic acidosis and hyperkalemia

Spironolactone (Aldactone®)

- Specific antagonist of mineralocorticoid receptor
  - Inhibits the increase in K^+ secretion mediated by the endogenous agonist aldosterone
- Sometimes spironolactone is used for its inhibitory actions on androgen and progesterone receptors
  - E.g., treatment of polycystic ovary disease
- Mortality benefit in severe CHF

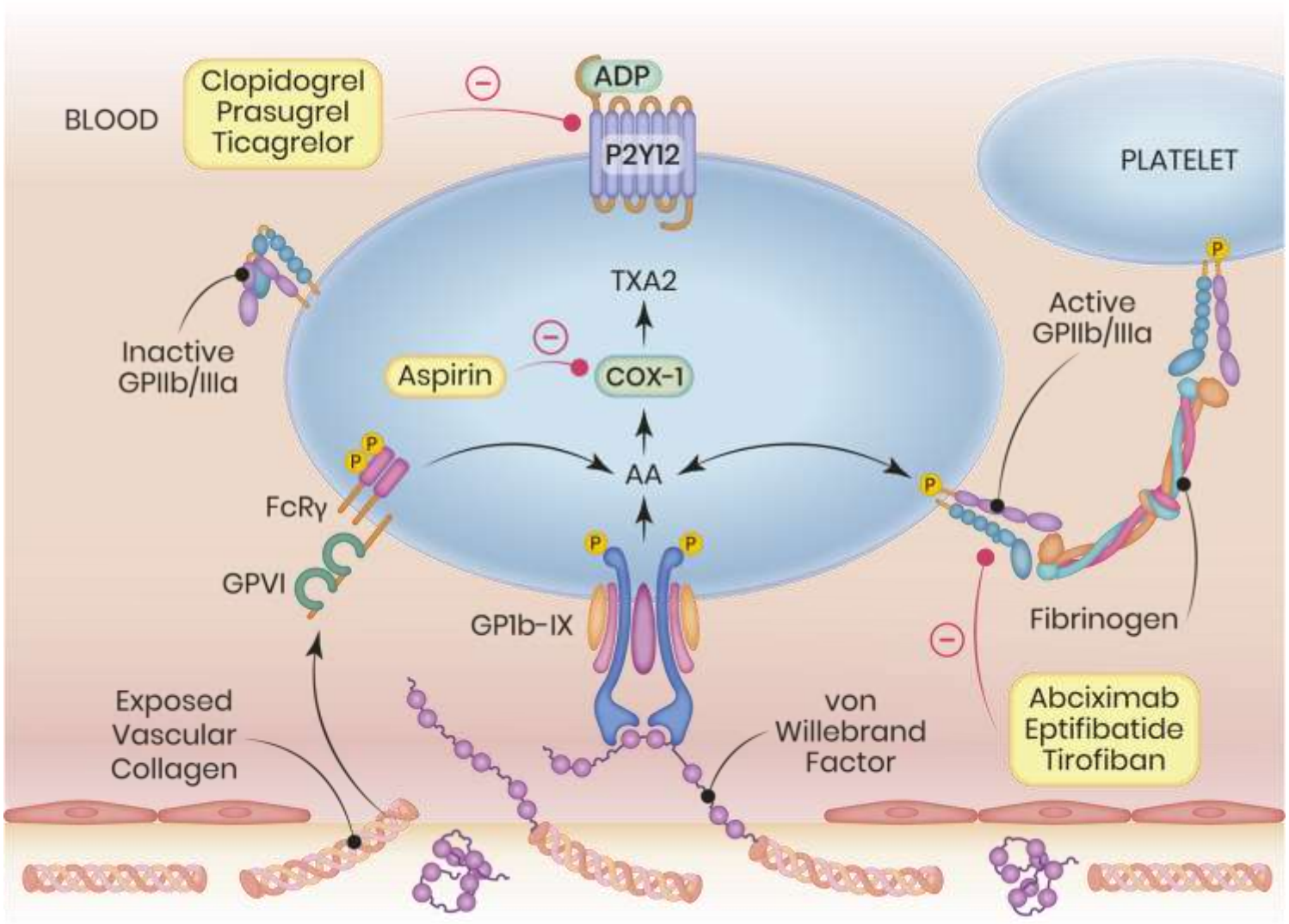
Spironolactone

- **Adverse effects:**
  - Hyperkalemia
    - Particularly if used alone
  - Steroid structure cross-reacts with other hormone receptors causing:
    - Gynecomastia
    - Impotence
    - Decreased libido
    - Hirsutism
    - Menstrual irregularities

Other Aldosterone Antagonists

- Eplerenone (Inspra®) – Weak diuretic with fewer anti-androgenic effects
  - Shown to have mortality benefit post-MI in patients with LV dysfunction (EPHESUS trial)
- Drospirenone (Yaz®) – contraceptive with weak anti-aldosterone effects
  - Synthetic progestin

Antiplatelet Drugs



Platelets

- Provide the initial hemostatic plug at sites of vascular injury.
  - Are generally more active on the arterial side of the vascular tree
- Play a role in pathological thromboses that lead to myocardial infarction, stroke, and peripheral vascular disease

- Prototype antiplatelet agent is Aspirin
  - Blocks production of thromboxane A_2 by permanently inhibiting COX-1 in platelets
  - TXA_2 promotes platelet aggregation and platelet aggregation
  - More about aspirin in later sections
- Aspirin is indicated in patients who have coronary disease or other significant atherosclerotic disease (carotid, cerebral, etc)

Platelet ADP Receptor (P2Y12) Antagonists

- ADP binds to P2Y12 receptor and activates platelets
  - (by decreasing cAMP!)
- Ticlopidine – prototype, no longer available due to hematologic side effects
  - TTP, aplastic anemia, agranulocytosis
- Clopidogrel (Plavix®) blocks ADP receptors on platelets
  - Pro-drug (converted to active form via CYP450 2C19
- Newer drugs: Prasugrel, Ticagrelor
  - Prasugrel – prodrug with less dependence on 2C19 (less genetic resistance
  - Ticagrelor – not a prodrug, has shown superiority to clopidogrel
- Given along with aspirin for patients with:
  - Acute MI
  - Ischemic CVA
- May be used alone in patients with aspirin allergy
- Required in patients who have a bare metal or drug-eluting coronary stent
- Rare adverse effects are *severe neutropenia and thrombocytopenia, bleeding events may occur as well*

Glycoprotein IIb/IIIa Inhibitors

- **GP IIb/IIIa** is a fibrinogen receptor/integrin on platelets
  - Defective in Glanzmann's thrombasthenia
- **Abciximab**
  - Fab fragment of a humanized monoclonal antibody directed against the IIb/IIIa receptor
  - Prevents platelet adhesion and aggregation
- **Eptifibatide**
  - Prevents binding of fibrinogen to the IIb/IIIa receptor
- Used in acute coronary syndromes, often in conjunction with coronary artery procedures
  - Generally only used for 18 hours or less
- Major adverse effect is bleeding

cAMP / cGMP Phosphodiesterase 3 Inhibitors

- Dipyridamole, Cilostazol
  - Increase cAMP in platelets (opposite of P2Y12 receptor), causing inhibition
  - Increase cAMP and cGMP in vascular smooth muscle, causing vasodilation
  - Used in patients with peripheral vascular disease (arterial atherosclerosis)

Anticoagulants

- Used both as treatment for hypercoagulability and as prophylaxis for patients at risk for clotting complications (e.g., patients with atrial fibrillation, mechanical heart valves, inherited clotting disorders)
  - Factor V Leiden
    - Variant more prone to clotting activation
  - Prothrombin variant
    - Excessively active prothrombin
  - Protein C or protein S deficiencies
    - Protein C and S are endogenous “anti-coagulants”

Unfractionated Heparin

- Large, water-soluble polysaccharide molecules of varying size
  - 15,000-20,000 Daltons
  - Does **not** cross placenta
- Must be given parenterally
  - For anticoagulation, given as a constant drip
  - For prophylaxis, given subcutaneously TID
- Increases activity of antithrombin III
  - This inactivates thrombin (IIa) and factor Xa
- Monitor by following aPTT
- Antidote = **protamine sulfate** (chemical antagonism)

Low Molecular Weight Heparin / Fondaparinux

- Purified heparin (MW 2000-6000)
  - Enoxaparin
- Fondaparinux
  - synthetic heparin with similar properties to LMWH
- Binds ATIII but only inhibits Factor Xa, not thrombin
- Given subcutaneously
  - No drip necessary, given daily for prophylaxis, twice daily for anticoagulation
- Cannot be monitored with aPTT
  - Because thrombin is not inhibited significantly
  - Use LMWH levels / Factor Xa levels
- Dosed by weight
  - Cannot be used in the morbidly obese
  - Cleared renally, so not for use in renal failure

Heparin

- **Clinical uses:**
  - Rapid anticoagulation for thromboses, pulmonary emboli, unstable angina, open heart surgery
  - “Bridge” to warfarin therapy
  - Anticoagulation of pregnant women
  - DVT prophylaxis in at-risk patients
- **Adverse effects:**
  - Bleeding
  - *Heparin-induced thrombocytopenia (HIT)*
    - Immune-mediated
  - Skin necrosis at site of injection
    - Probably immune-mediated

Heparin-Induced Thrombocytopenia (HIT)

- “Heparin Allergy”
- Patients receiving heparin for anticoagulation generate antibodies against heparin that cross-react with PF4 (platelet-factor 4)
- Antiboties cause platelet destruction
  - And/Or Activation!
- Diagnosis : PF4 Elisa and SRA (serotonin-release Assay)
- Treatment: Stop heparin and start direct thrombin inhibitor (i.e. argatroban)

Warfarin (Coumadin®)

- Given orally
- Half-life approximately 30 hours
- Metabolized by cytochrome P450 (CYP) 2C9 in liver
  - *Many drug-drug interactions*
- Contraindicated in pregnancy (category X)
  - Crosses placenta
  - Teratogenic

Warfarin

- Decreases hepatic synthesis of vitamin K-dependent clotting factors (II, VII, IX, X, protein C, protein S)
  - Remember that C and S are anticoagulants
- Monitored by prothrombin time (PT)
  - Standard assay is INR (international normalized ratio)
- Antidotes for overdose
  - Vitamin K
    - Slower acting
    - Need to wait for production of new clotting factors
  - Fresh frozen plasma
    - Provides clotting factors if immediate correction needed for severe bleeding

Warfarin

- **Clinical uses:**
  - Long term anticoagulation for patients at high risk for thromboemboli (congenital thrombopathies, mechanical heart valves, atrial fibrillation)
  - Patients with known DVT
  - Patients with large anterior myocardial infarction with hypokinesis of the ventricle

Warfarin

- **Drug and diet interactions:**
  - Warfarin interacts with a prodigious number of other drugs and its effect is influenced by diet
  - Warfarin effect countered by diet high in vitamin K (e.g., spinach, greens)
- **Adverse effects:**
  - Bleeding
  - *Skin necrosis*
  - Teratogenic (contraindicated in pregnancy)
  - Multiple drug interactions

Warfarin

- Warfarin-indeuced skin necrosis
  - Results from paradoxical, transient hypercoagulable effect of early warfarin therapy
    - Protein C has the shortest half-life of the vitamin K-dependent factors
  - Prevented by starting patient on heparin and warfarin initially and then switching to warfarin alone
    - Provides protection (“bridge”) in the temporary hypercoagulable period
  - Patients with this condition should have their warfarin dose lowered and be put on heparin, consider fresh frozen plasma if no improvement

Direct Thrombin Inhibitors

- Argatroban
  - Inhibits thrombin directly
  - Alters both PT and aPTT, aPTT is used for monitoring
  - No antidote available
  - Must be carefully titrated in patients with liver failure

- Dabigatran
  - Oral form of argatroban (first oral anticoagulant since warfarin (1940's)
  - Reversal agent – monoclonal antibody

- Lepirudin
  - Derived from hirudin, a direct thrombin inhibitor from the medicinal leech
  - Monitored by daily aPTT
  - No antidote available
  - Use cautiously in renal failure (cleared by kidneys)

Factor Xa inhibitors

Rivaro**xa**ban

Edo**xa**ban

Api**xa**ban

- Oral anticoagulants for treatment and prophylaxis of DVT/PE, stroke prophylaxis in patient with atrial fibrillation
- Rapid onset
- Antidote is Andexanet Alfa (recombinant factor X molecule)
- Adverse effects : bleeding

Thrombolytics

- The fibrinolytic system dissolves intravascular clots as a result of the action of plasmin, an enzyme that digests fibrin
- The thrombolytics in clinical use
  - Tissue plasminogen activator (t-PA) (alteplase, tenecteplase)
  - Causes cleavage of plasminogen and production of plasmin
  - Plasmin digests fibrin
- Thrombolytics actively dissolve clots while anticoagulants only prevent clot growth and allow the body's natural plasmin system to dissolve the clot

Thrombolytics

- Given intravenously for emergency management of coronary thromboses, deep venous thromboses, pulmonary embolism, and thromboembolic strokes
- Main factor in the effectiveness of these agents is how quickly they are administered
- Adverse effects:
  - Major adverse effects are bleeding and hemorrhage
  - Especially when used with heparin
  - Can try to reverse with *tranexamic acid, aminocaproic acid* (anti-fibrinolytic agent) or fresh frozen plasma
  - *Thrombolytic therapy is contraindicated in situations where risk of hemorrhage is great.*

Contraindications to Thrombolytic Therapy

1. Surgery within 10 days
2. Serious GI bleed within last 3 months
3. History of hypertension with diastolic pressure > 110 mm Hg
4. Active bleeding or hemorrhagic disorder
5. Previous CVA or active intracranial process
6. Aortic dissection

Neuro-Pharmacology

Sedative-Hypnotic Drugs

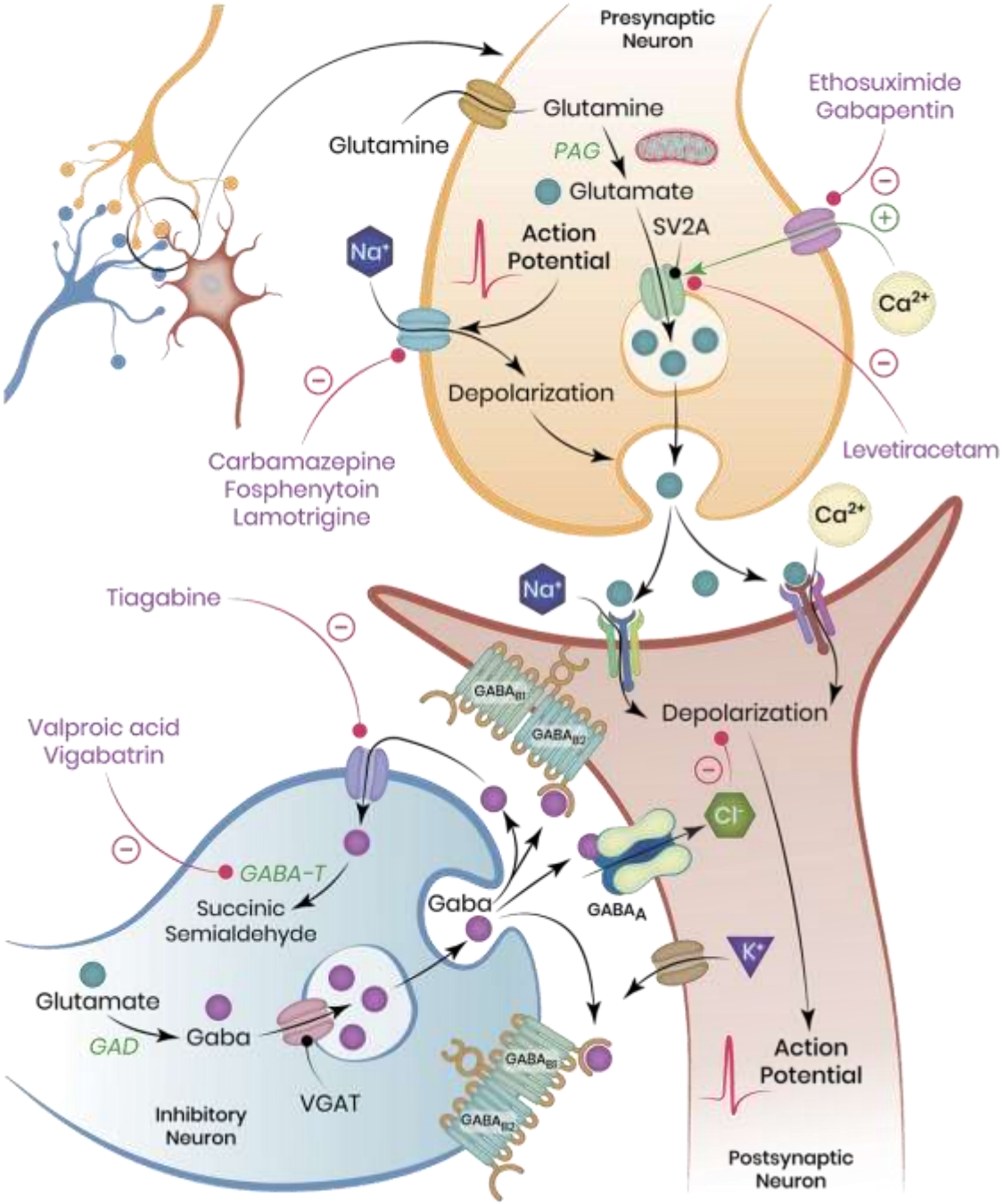
GABA

- Neurotransmitter metabolized from Glutamate via GAD (glutamic acid decarboxylase) (B6-dependent)
  - Metabolized via GABA transaminase back to glutamic acid / succinic semialdehyde

- *Inhibitory* neurotransmitter which activates two classes of receptors
  - $GABA_A$ receptors
  - $GABA_B$ receptors

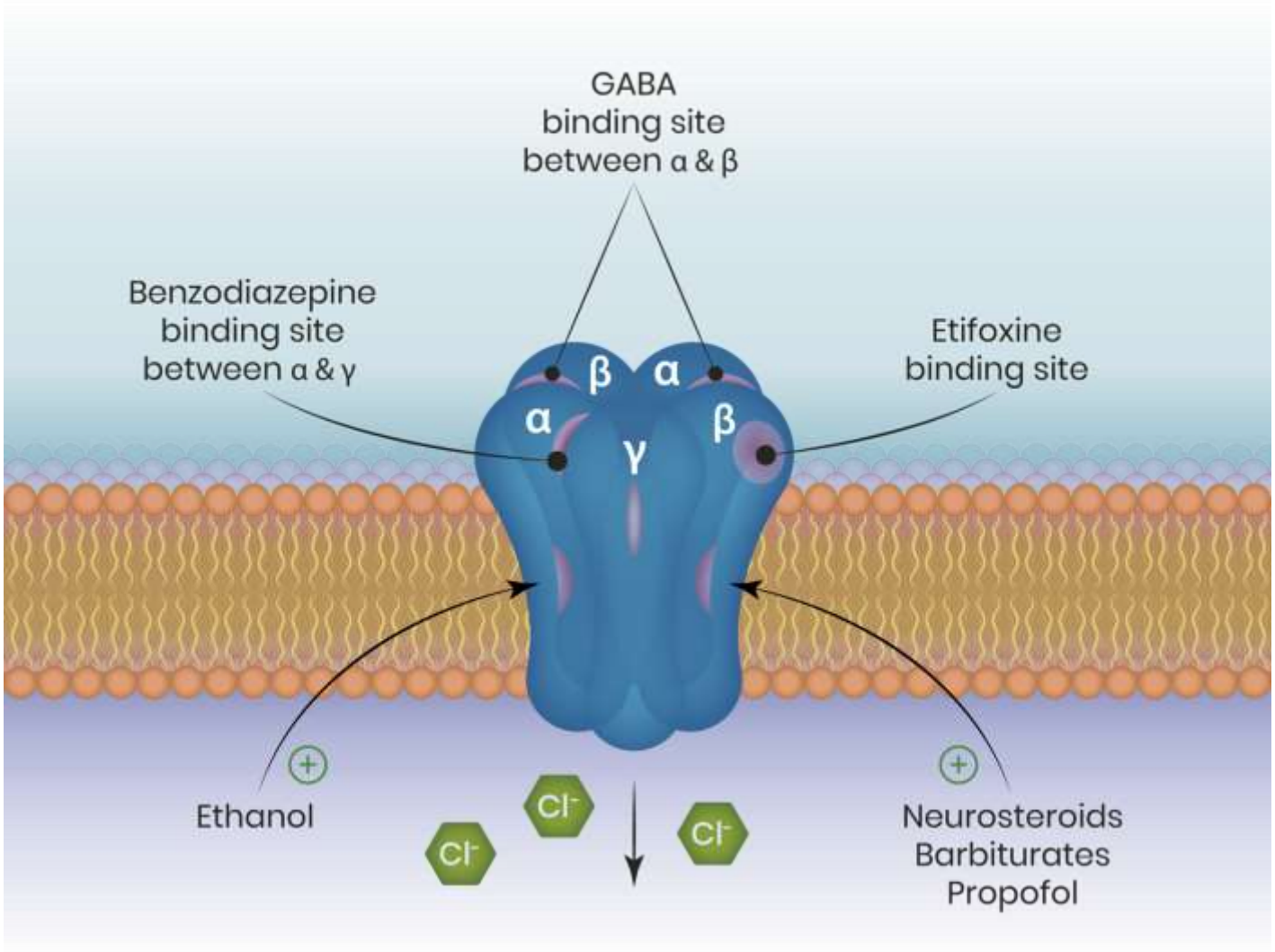
$GABA_A$ Receptors

- Ligand-gated chloride channels
- Molecular targets of:
  - Many general anesthetics (e.g., propofol)
  - Some sedative-hypnotics (e.g., diazepam)
  - Some anticonvulsants (e.g., phenobarbital)
- Binding of GABA results in hyperpolarization of the postsynaptic neuron



GABAergic Terminal

$GABA_A$ Receptor Structure



$GABA_B$ receptors

G-protein coupled receptors which are the target of some muscle relaxants

- baclofen, γ-hydroxybutyrate

- $G\alpha_i$ – coupled
  - GABA binding results in decreased cAMP / decreased Ca^{++} channel opening (inhibitory effect)
- Directly coupled to K^+-channels
  - GABA binding opens K^+-channels, leading to hyperpolarization of the neuron

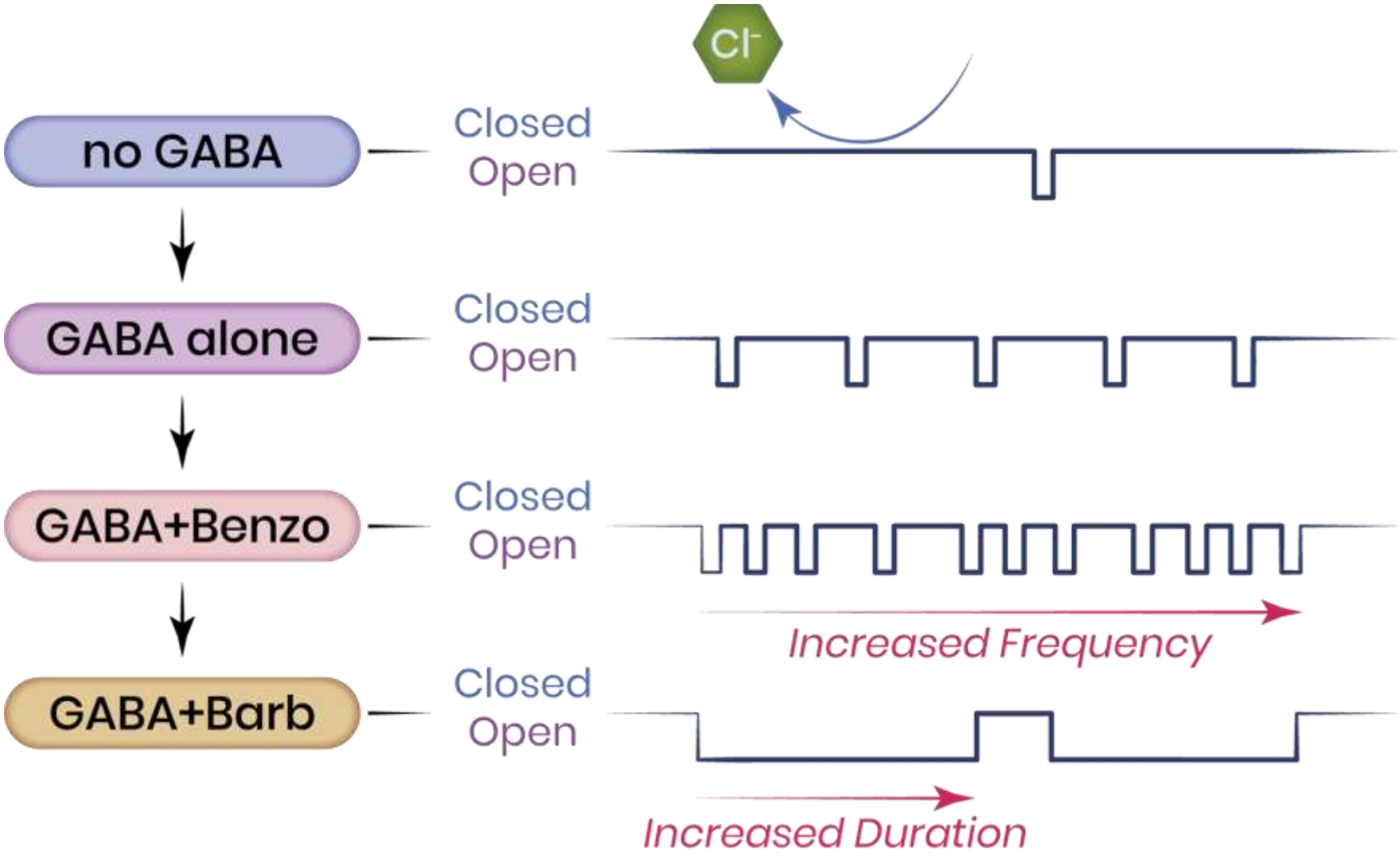
Sedative-Hypnotic Drugs

- *Sedation* related to decreased anxiety and motor activity
- *Hypnotic* effect related to induction of sleep / amnesia.
- Include benzodiazepines, barbiturates, and alcohols (e.g., chloral hydrate)
- Cause respiratory depression in overdose
- Older sedative-hypnotics such as barbiturates and chloral hydrate far more dangerous in overdose than the benzodiazepines

Sedative-hypnotics – mechanism of action

- Most enhance the actions of GABA at the inhibitory $GABA_A$ receptors
  - Lead to stronger hyperpolarization of the target neuron, decreased likelihood of that neuron sending an action potential.
- Benzodiazepines potentiate GABA by increasing the *frequency* of chloride ion channel opening
- Barbiturates increase the *duration* of chloride ion channel opening of $GABA_A$ receptors

Effect of benzodiazepines and barbiturates on $GABA_A$ receptor channel activity



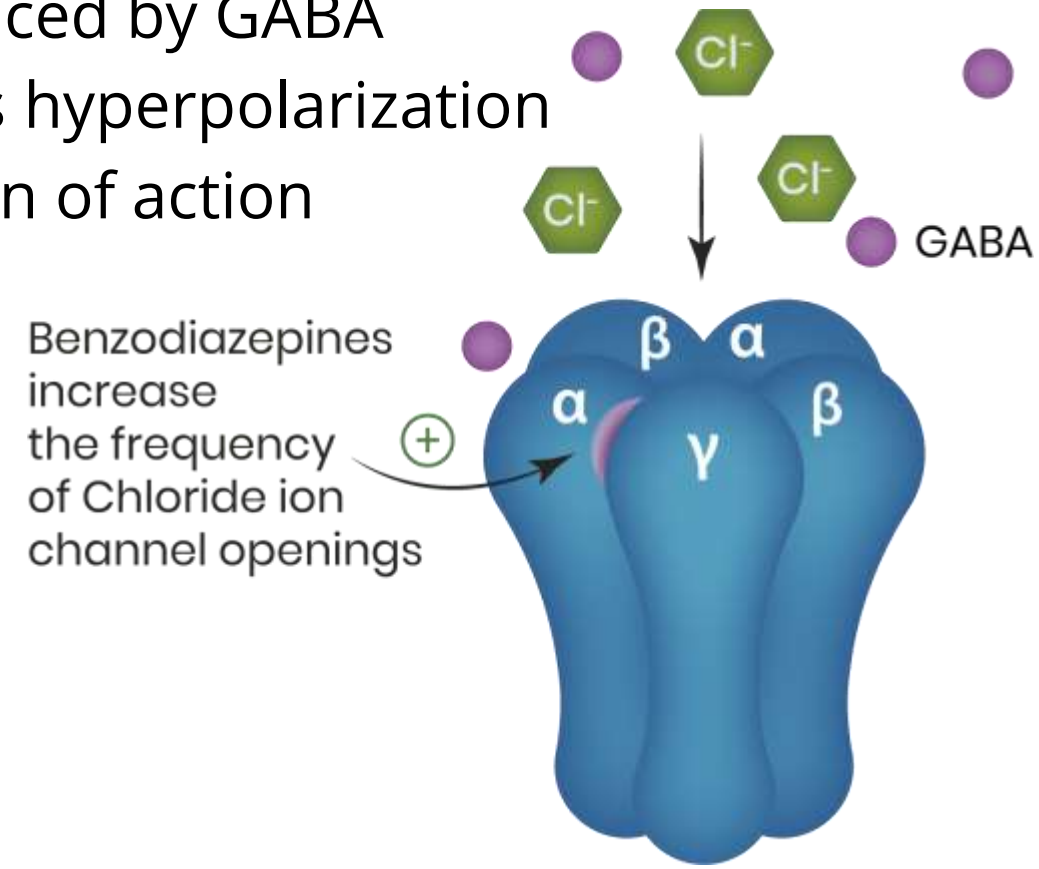
Sedative-hypnotics – antidotes

- Only the benzodiazepines have a specific antidote (*flumazenil*) referred to as a benzodiazepine receptor antagonist.

- ****_No_ specific antidote for barbiturate overdose****

Benzodiazepines

- γ-aminobutyric acid ($GABA_A$) receptors
  - Between α subunit and the γ subunit
- Increase the *frequency* of chloride ion channel openings produced by GABA
  - chloride influx causes hyperpolarization
  - inhibits the generation of action potentials



Therapeutic Uses

- **Short-term Treatment of Anxiety Disorders** (SSRIs are used in long-term treatment)
- **Insomnia** (difficulty falling or staying asleep)
- **Seizures** Benzodiazepines increase seizure threshold by hyperpolarizing CNS
  - **Lorazepam** and **diazepam** most frequently used via IV.

Therapeutic Uses

Preanesthetic due to anxiolytic, sedative, and anterograde amnestic properties
  - Shorter-acting benzodiazepines (e.g., midazolam)
- **Muscle relaxation.** Diazepam can treat muscle spasms and spasticity
- **Withdrawal states** (delirium tremens)
- Agitation in **Acute mania**

Adverse effects

- Physical and Psychological Dependence
- Respiratory Depression
- Daytime drowsiness and sedation
- Rebound insomnia
- Relatively safe in overdose
  - Can be dangerous in combination with other CNS depressants
  - Flumazenil is antidote

Specific Benzodiazepines

- Alprazolam (Xanax®)
  - Treatment of anxiety, panic, phobias
- Diazepam (Valium®)
  - Treatment of anxiety, seizures; sedation
  - Long-acting
- Clonazepam (Klonopin®)
  - Anti-convulsant
  - Treatment of anxiety
  - 3 active metabolites
- Midazolam (Versed®)
  - Short-acting
  - Pre-operative sedation
  - Anterograde amnesia

Specific Benzodiazepines

Half-Life		Primary Indications
Short-acting ($t_{1/2}$ < 5 hrs)	**Midazolam****	Preanesthetic
	Triazolam	Insomnia, preanesthetic
Intermediate-acting ($t_{1/2}$ = 5–24 hrs)	**Alprazolam****	Anxiety, antidepressant
	Clonazepam**	Seizures
	Estazolam	Insomnia
	Lorazepam	Anxiety, insomnia, seizures, preanesthetic
	Oxazepam	Anxiety
	Temazepam	Insomnia
Long-acting ($t_{1/2}$ > 24 hrs)	**Chlordiazepoxide**	Anxiety, preanesthetic, withdrawal states
	Clorazepate	Anxiety, seizures
	Diazepam**	Anxiety, preanesthetic, seizures, withdrawal states
	Flurazepam	Insomnia
	Prazepam	Anxiety
	Quazepam	Insomnia

Barbiturates

- Multiple clinical uses
  - Sedative-hypnotics (replaced by benzodiazepines)
  - Anticonvulsants (phenobarbital)
    - Tonic-clonic seizures, status epilepticus, and eclampsia.
    - Recurrent febrile seizures.
  - Anesthetic induction (thiopental)

- Dangerous in overdose
  - No specific antidote

Barbiturates

- Classified according to the rate of onset and duration of the therapeutic action.
  - Ultra-Short Acting
    - Thiopental (anesthesia)
  - Short Acting
    - Pentobarbital Secobarbital Amobarbital
  - Long Acting
    - Phenobarbital (seizures)

Barbiturates

- Bind $GABA_A$-receptor chloride channel, but at a different binding site than for benzodiazepines

- *Prolong* opening of GABA chloride channels

Barbiturates – adverse effects

- Induction of hepatic CYP450 metabolism
  - Especially seen with phenobarbital
  - Drug-drug interactions
- Can block complex I of the electron transport chain
- Also induce δ-aminolevulinic acid synthase, key enzyme in heme synthesis
  - Contraindicated in patients with hepatic porphyria

Barbiturates – adverse effects

- Depression of CNS:
  - Low doses induce sedation (drowsiness, impaired concentration, and mental and physical sluggishness).
  - Higher doses induce hypnosis, followed by anesthesia (loss of feeling or sensation)
  - Over dosage can lead to coma and death.
  - Have no analgesic properties.
  - The CNS depressant effects of barbiturates synergize with those of *ethanol*.

Barbiturates - abuse

- Chronic use leads to tolerance and dependence
- Sudden withdrawal of short-acting barbiturates leads to severe withdrawal symptoms
  - Anxiety
  - Agitation
  - Hyperreflexia
  - Seizures

Chloral hydrate

- Chloral hydrate
  - Older, alcohol sedative-hypnotic
  - Used for sedation of children prior to procedures
  - Dangerous in overdose
  - No specific antidote

Other sedative-hypnotics

- Zolpidem (Ambien®), zaleplon (Sonata®), and eszopiclone (Lunesta®) ("Z-drugs")
  - Non-benzodiazepines, but bind to α1-containing GABA-receptors
    - Binding site is very close to benzodiazepine binding site
    - Flumazenil has been shown to reverse Z-drugs
  - Effective short-term sleep aids
  - Less abuse liability than other sedative-hypnotics
- Ramelteon
  - Agonist at Melatonin Receptors MT_1 and MT_2 in suprachiasmatic nucleus of hypothalamus.
  - Effective at inducing sleep
  - Can cause hyperprolactinemia
- Suvorexant
  - OX1/OX2 receptor antagonist
  - Effective for treating insomnia
  - Orexin A and B normally bind to OX1/OX2 receptors and stimulate arousal centers in the brain stem

Antiepileptics

Seizures

- Episodic electrical discharges in cerebral neurons associated with prolonged depolarization
- Can involve the entire brain (generalized) or only specific brain regions (partial)
- The goal of drug management is to restore normal patterns of electrical activity

Seizure Medications

- Tonic Clonic
  - Phenytoin
  - Carbamazepine
  - Valproic Acid
  - Lamotrigine
- Absence
  - Ethosuximide
  - Valproic Acid
  - Clonazepam
- Myoclonic
  - Valproic Acid
  - Clonazepam
  - Lamotrigine
- Additional Meds
  - Gabapentin
  - Lamotrigine
  - Phenobarbital
  - Levetiracetam

Phenytoin (Dilantin®)

- Commonly used anticonvulsant
- Blocks voltage-gated Na^+ ion channels in inactivated state ("state"-dependent blockade)
  - The more nerve firing, the more the drug is able to bind the channel
- Effective in partial seizures and also in general tonic-clonic seizures

Different states of an ion channel

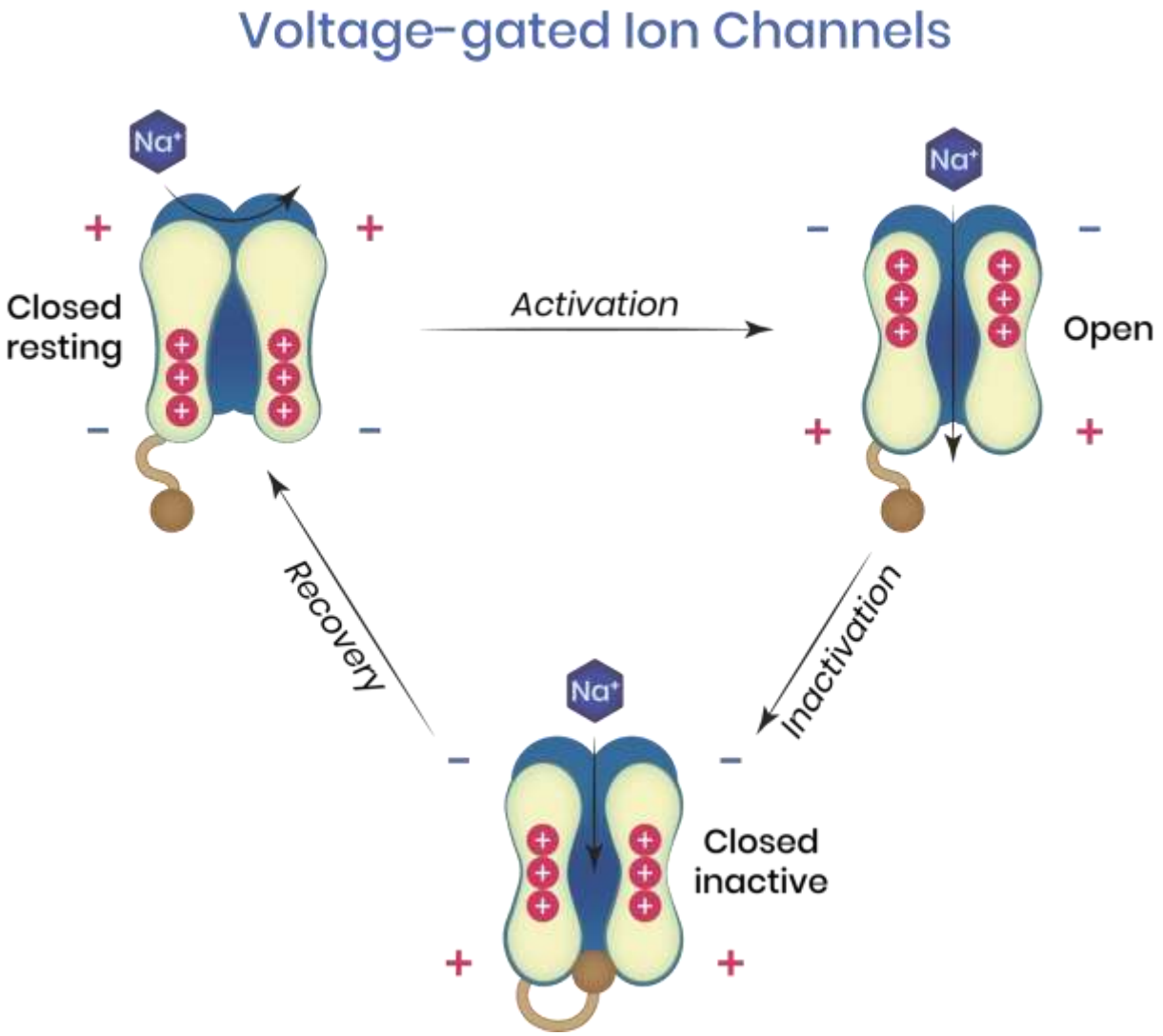
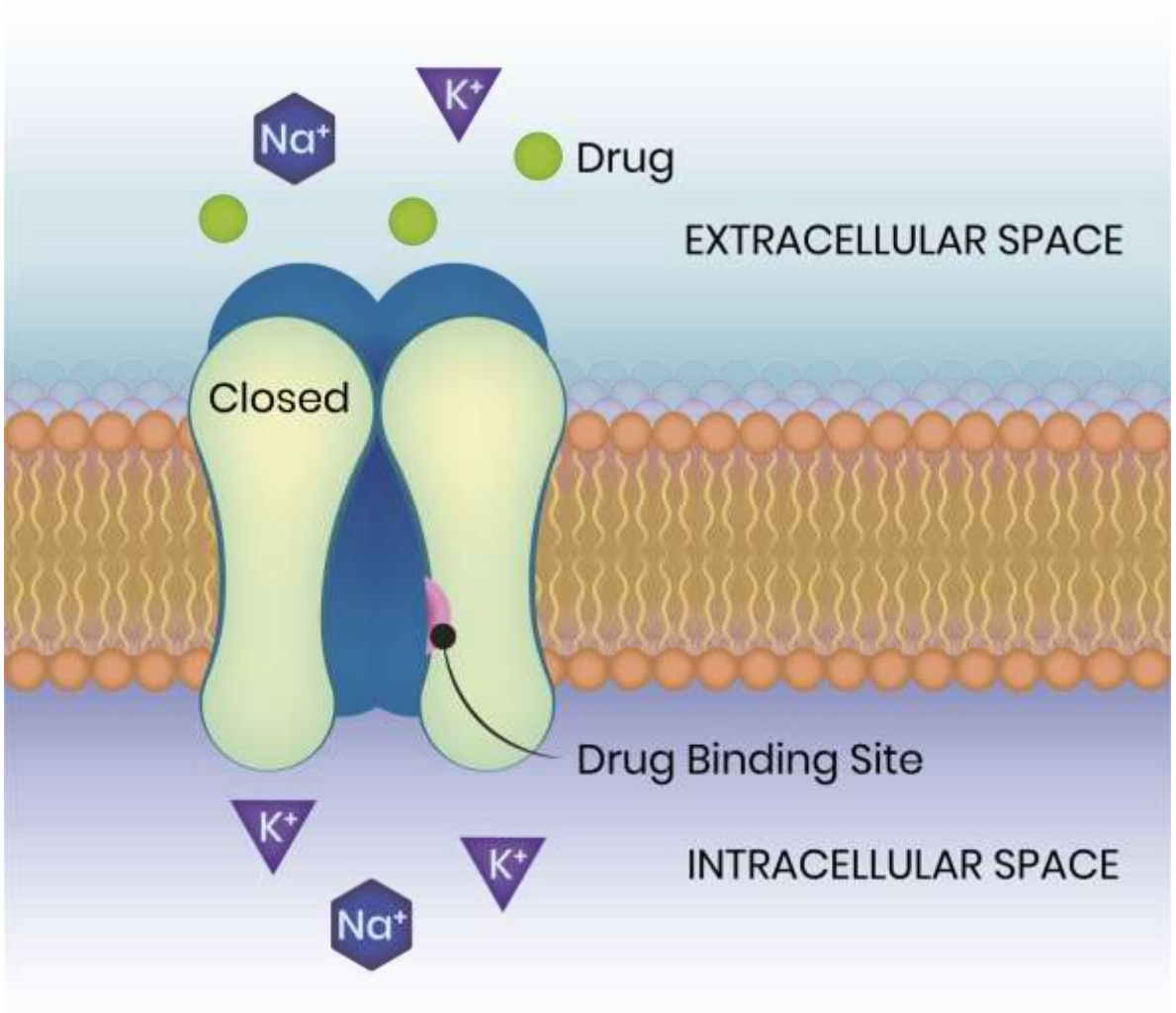
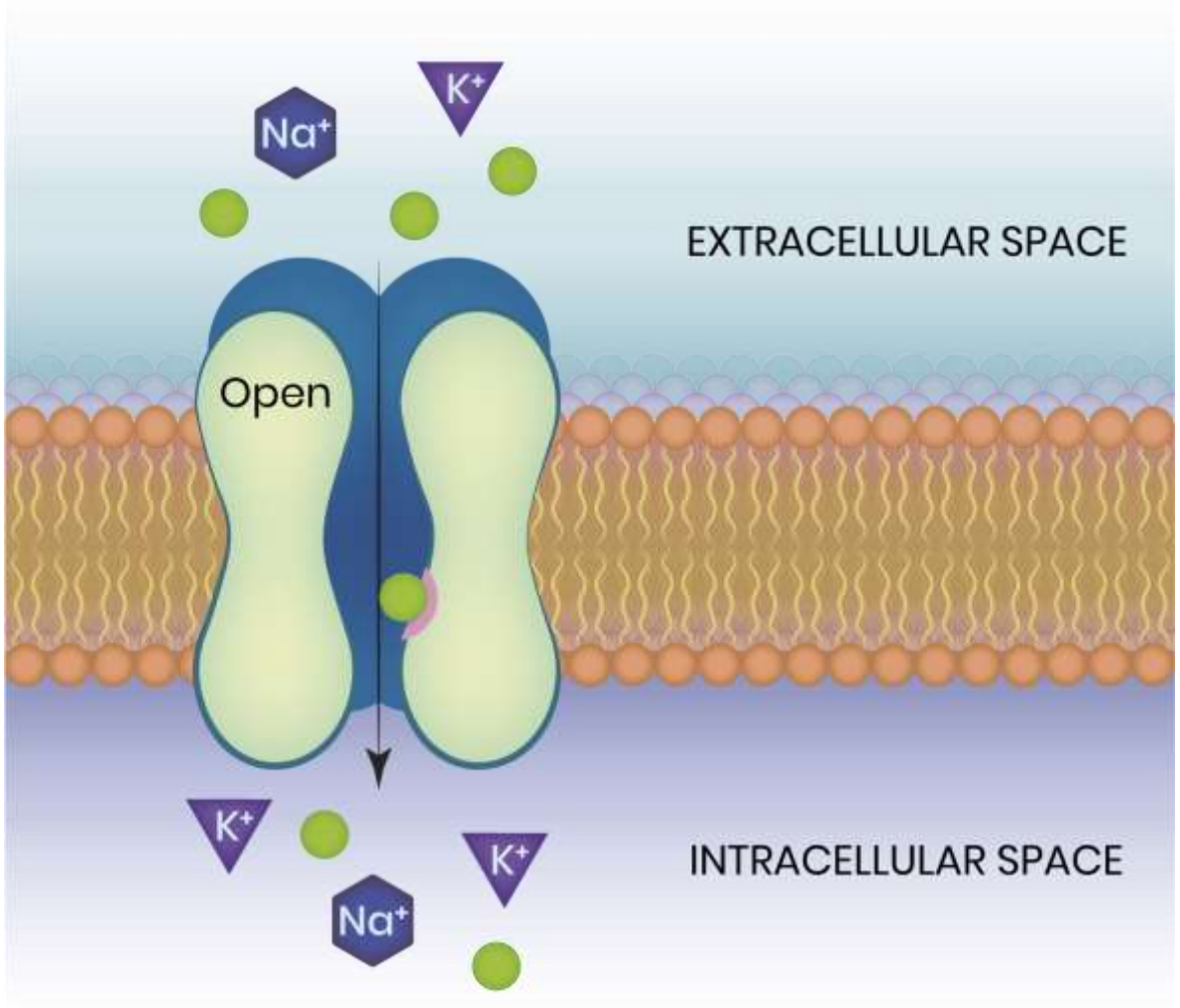


Illustration of state-dependent blockade



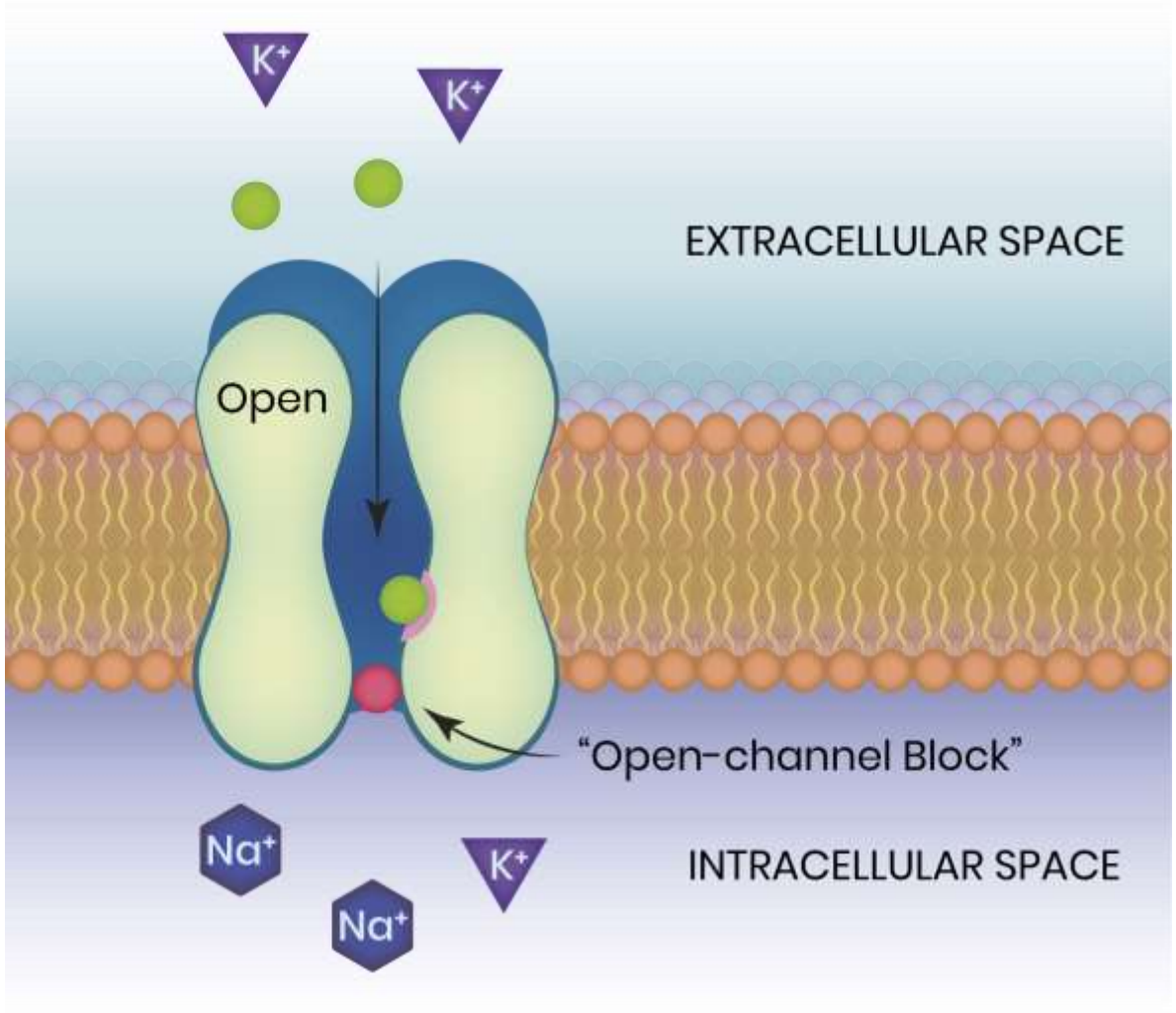
Drug is unable to interact with channel in closed state

Illustration of state-dependent blockade



Drug binding site is accessible in open state of channel

Illustration of state-dependent blockade

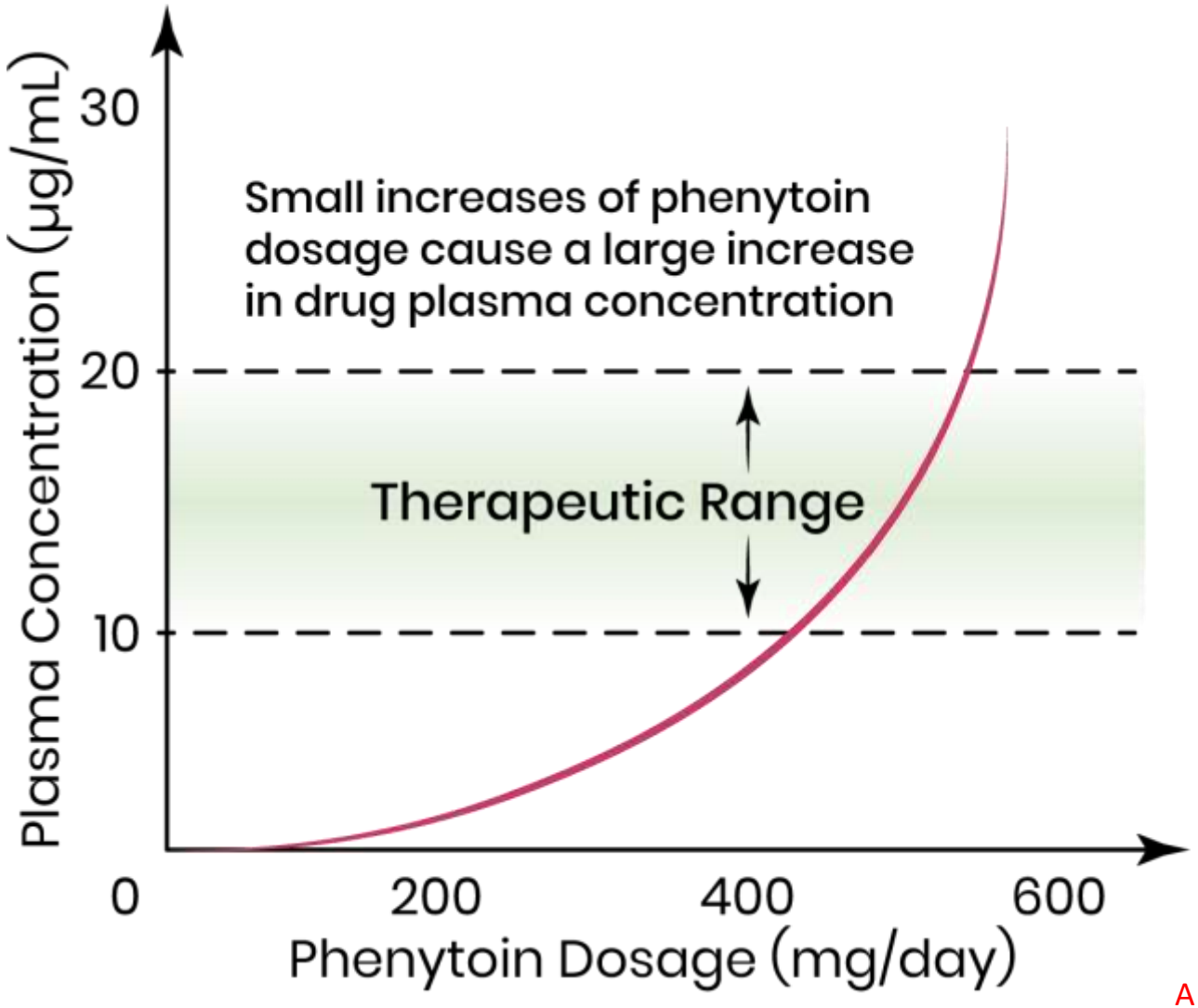


Channel blocked

Phenytoin – pharmacokinetics

- Very difficult drug to dose
  - Zero-order elimination kinetics
- First-pass metabolism
- Inducer of multiple CYP enzymes

Phenytoin's zero-order elimination kinetics



A copy from Unit 1

Phenytoin – adverse effects

- Sedation
- Ataxia
- Diplopia
- *Gingival overgrowth*
- Osteomalacia
  - More rapid metabolism of vitamin D
- Dermatologic reactions (including Stevens-Johnson type)
- Pseudolymphoma syndrome
- Drug-induced Lupus
- Block of insulin release from islet cells
- Pain on injection
  - IV solution is approximately pH 12 (!)

Fetal Hydantoin Syndrome

- Phenytoin associated with birth defects when used by mothers in the first trimester of pregnancy
  - Cleft palate
  - Digit abnormalities
  - Microcephaly, facial abnormalities
  - Congenital heart defects (VSD, pulmonic stenosis, TGA)

Fosphenytoin

- Water-soluble analog of phenytoin
- Used IV for status epilepticus
  - Can be infused much more quickly than phenytoin IV

Carbamazepine (Tegretol®)

- Similar mechanism of action to phenytoin
- Similar pharmacokinetics to phenytoin
- Also drug of choice for trigeminal neuralgia and used to treat bipolar syndrome

Carbamazepine – adverse effects

- Similar to phenytoin except no gingival overgrowth
- Commonly causes mild SIADH
- Induces its own metabolism
  - P450 inducer
- SJS, aplastic anemia
- Teratogenicity (neural tube defects, cleft lip, congenital heart defects)

Ethosuximide

- Blocks T-type Ca^{2+} ion currents in thalamic neurons

- Very effective for absence seizures

Valproic acid

- Unclear mechanism of action
  - Putative actions:
    - Inhibiting GABA transaminase (Decreased GABA Production)
    - Inhibiting T-type Ca++ channels
    - Inhibiting voltage gated sodium channels
    - Inhibiting HDAC (histone deacetylase)
- Also used for bipolar disorder, schizophrenia and migraine headaches

Valproic acid – adverse effects

- Hepatotoxicity
  - Monitor hepatic enzymes periodically
- Pancreatitis
- Alopecia
- Thrombocytopenia
- Potentially teratogenic
  - Associated with fetal spina bifida
- Causes weight gain
- Less p450 activity, does inhibit CYP2C9

Other anti-convulsants

- *Lamotrigine* (Lamictal®)
  - Inhibits voltage-gated sodium channels
  - Used for wide variety of seizures includes absence seizures
  - *High rate of dermatologic reactions (SJD)*
  - *Excellent safety record in pregnancy*

- *Levetiracetam (Keppra®)*
  - Mechanism unclear
  - Generally used as a first-line seizure drug in mild seizures given its low risk profile
  - Pregnancy category C
  - Causes somnolence and neuropsychiatric symptoms in 5-10% of patients

Other anti-convulsants

- *Topiramate*
  - Blocks AMPA receptors, sodium and calcium channels
  - Weak inhibitor of carbonic anhydrase
- *Vigabatrin*
  - Irreversible inhibitor of enzyme that degrades GABA
  - Can cause visual field defects

Drugs for tonic-clonic seizures

- Phenytoin
- Carbamazepine
- Phenobarbital
- Valproic acid
- Levetiracetam

Drugs for absence seizures

- *Ethosuximide*
- Valproic acid
- Clonazepam
- Lamotrigine

Drugs for status epilepticus

- *Fosphenytoin*
- Diazepam
  - Sometimes given *per rectum* to children
- Lorazepam
- Phenytoin