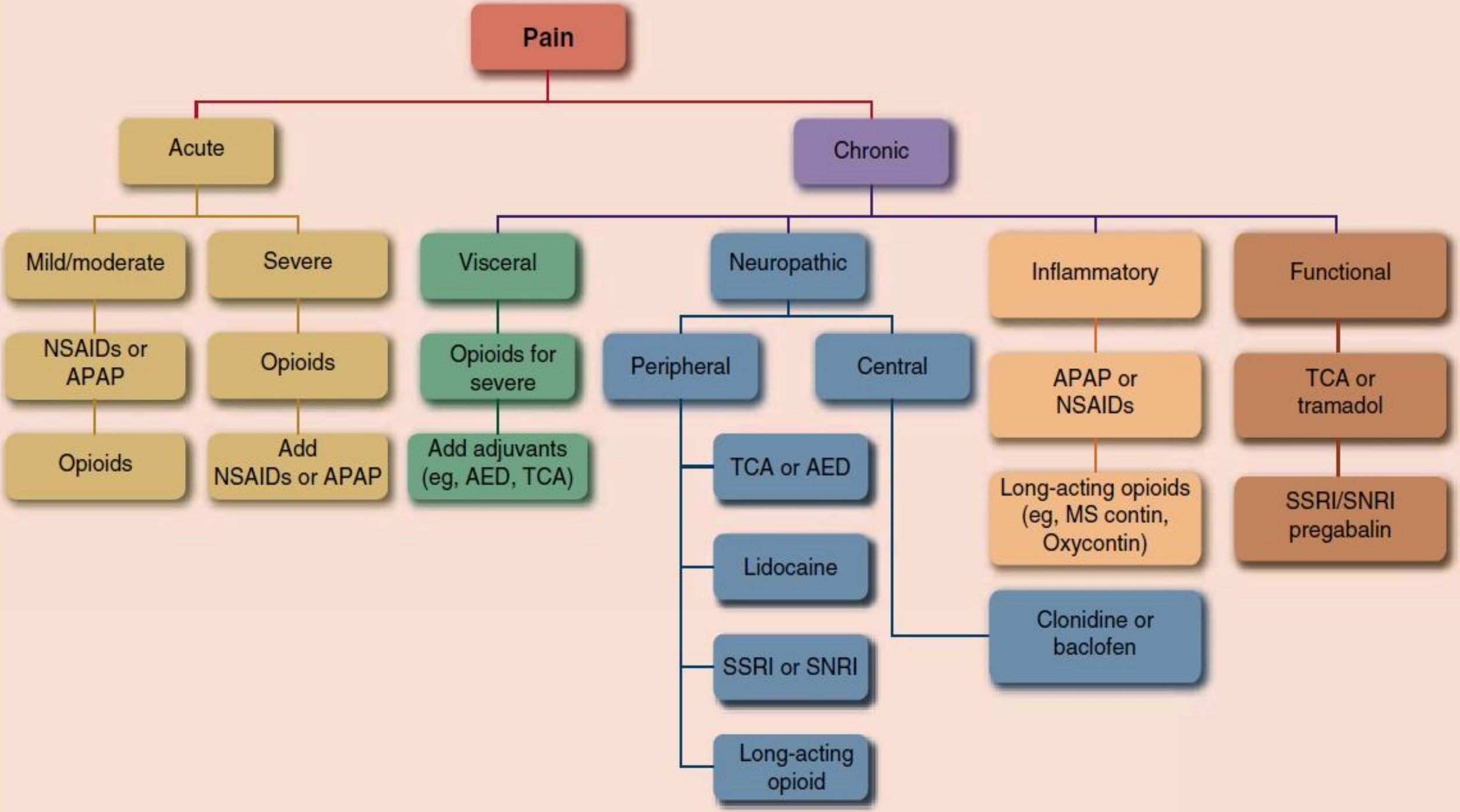
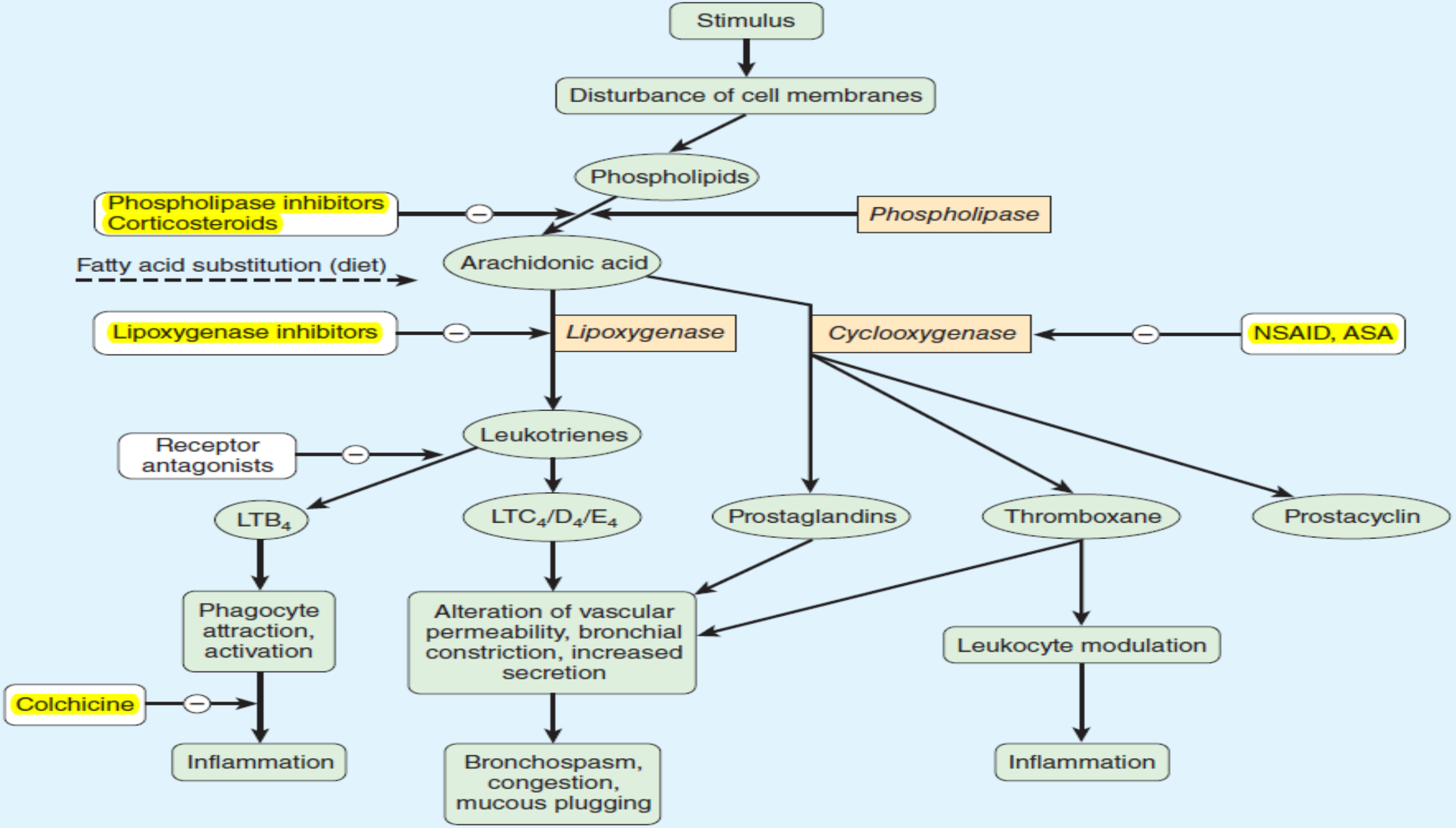

Pain
Acute
Chronic
Mild/moderate
Severe
NSAIDs or APAP
Opioids
Opioids
Add NSAIDs or APAP
Visceral
Neuropathic
Inflammatory
Functional
Opioids for severe
Add adjuvants (eg, AED, TCA)
Peripheral
Central
APAP or NSAIDs
TCA or tramadol
TCA or AED
Lidocaine
SSRI or SNRI
Long-acting opioid
Long-acting opioids (eg, MS contin, Oxycontin)
SSRI/SNRI pregabalin
Clonidine or baclofen


Stimulus
Disturbance of cell membranes
Phospholipids
Phospholipase inhibitors
Corticosteroids
Phospholipase
Fatty acid substitution (diet)
Arachidonic acid
Lipoxygenase inhibitors
Lipoxygenase
Cyclooxygenase
NSAID, ASA
Leukotrienes
Receptor antagonists
LTB4
LTC4/D4/E4
Prostaglandins
Thromboxane
Prostacyclin
Phagocyte attraction, activation
Alteration of vascular permeability, bronchial constriction, increased secretion
Leukocyte modulation
Colchicine
Inflammation
Bronchospasm, congestion, mucous plugging
Inflammation

Most nonsteroidal antiinflammatory drugs (NSAIDs) are nonselective inhibitors of cyclooxygenases, acting on both COX 1 and COX 2 isoforms to decrease formation of PGs and thromboxanes.

- Are analgesic, antipyretic, and antiinflammatory
- Have antiplatelet effects
- Acetylsalicylic acid (ASA) is prototype of the group, which includes more than 20 individual drugs

# ACETYLSALICYLIC ACID (ASA; ASPIRIN)

High-Yield

- Causes irreversible inhibition of COX
- Covalent bond via acetylation of a serine hydroxyl group near the active site
- Actions are dose-dependent:

**Antiplatelet aggregation**. Low dose, the basis for post-MI prophylaxis and to reduce the risk of recurrent TIAs

**Analgesia and antipyresis**. Moderate dose

**Antiinflammatory**. High doses

**Uric acid elimination**

- Low to moderate doses: ↓ tubular secretion → hyperuricemia
- High doses: ↓ tubular reabsorption → uricosuria

**Acid-base and electrolyte balance**

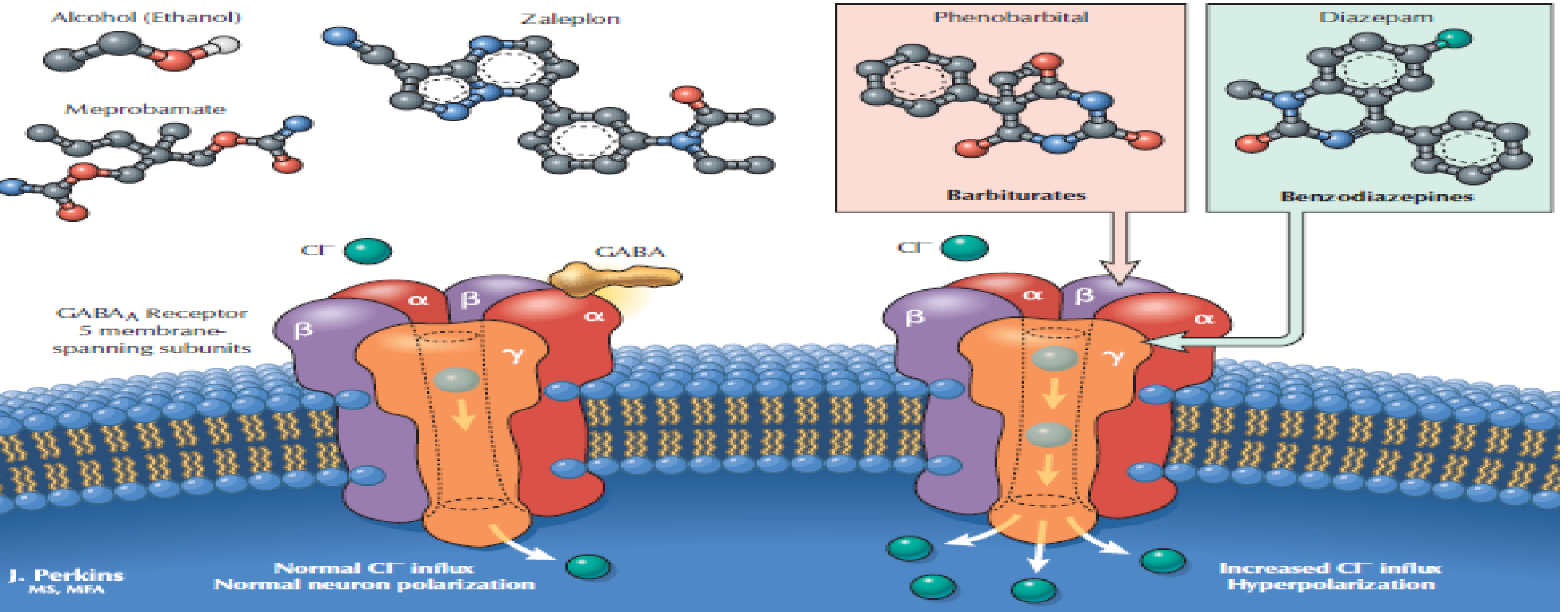
- Dose-dependent actions
- High therapeutic: mild uncoupling of oxidative phosphorylation →↑ respiration →↓ $pCO_2$→**respiratory alkalosis**→ renal compensation →↑ $HCO_3^-$ elimination →**compensated** respiratory alkalosis (pH = normal, ↓ $HCO_3^-$, ↓ $pCO_2$)
- In adults, this can be a stable condition; in children →↑ toxicity.
- Toxic doses: inhibits respiratory center →↓ respiration →↑ $pCO_2$→**respiratory acidosis** (↓ pH, ↓ $HCO_3^-$, normalization of $pCO_2$) plus inhibition of Krebs cycle and severe uncoupling of oxidative phosphorylation (↓ ATP) →**metabolic acidosis**,

# ACETAMINOPHEN

High-Yield

- Mechanisms:
  - No inhibition of COX in peripheral tissues and lacks significant antiinflammatory effects
  - Equivalent analgesic and antipyretic activity to ASA due to inhibition of cyclooxygenases in the CNS
- Comparisons with ASA:
  - No antiplatelet action
  - Not implicated in Reye syndrome
  - No effects on uric acid
  - Not bronchospastic (safe in NSAID hypersensitivity and asthmatics)
  - Gastrointestinal distress is minimal at low to moderate doses
- Overdose and management:
  - Hepatotoxicity—Acetaminophen is metabolized mainly by liver glucuronyl transferase to form the inactive conjugate. A minor pathway (via P450) results in formation of a reactive metabolite (*N*-acetylbenzoquinoneimine), which is inactivated by glutathione

| Selected Sedative-Hypnotics | | | | | |
|---|---|---|---|---|---|
| **Class** | **Drug** | **Class** | **Drug** | **Class** | **Drug** |
| Alcohols | Ethanol<br>Chloral hydrate | Benzodiazepines | Alprazolam<br>Chlordiazepoxide<br>Clorazepate<br>Diazepam<br>Flurazepam<br>Lorazepam<br>Oxazepam<br>Prazepam<br>Temazepam<br>Triazolam | Carbamates | Meprobamate |
| Barbiturates | Amobarbital<br>Aprobarbital<br>Mephobarbital<br>Pentobarbital<br>Phenobarbital<br>Secobarbital<br>Thiopental | | | Miscellaneous | Buspirone<br>Zaleplon<br>Zolpidem |

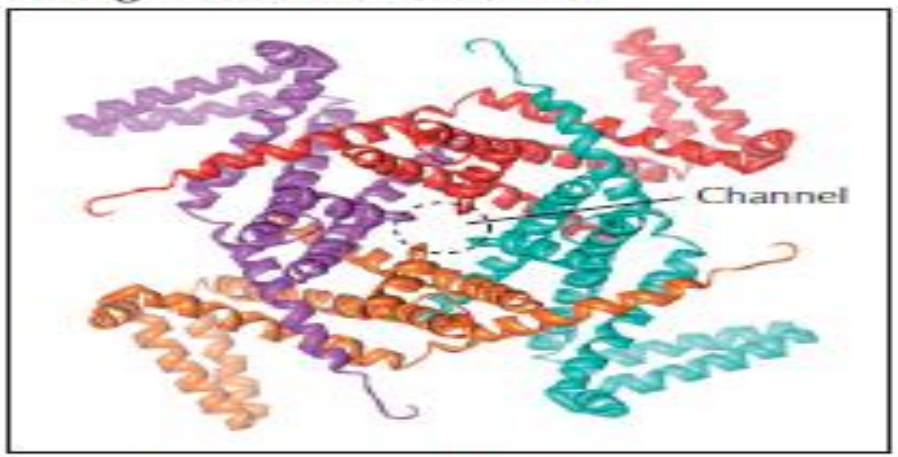


## Selected Local Anesthetics

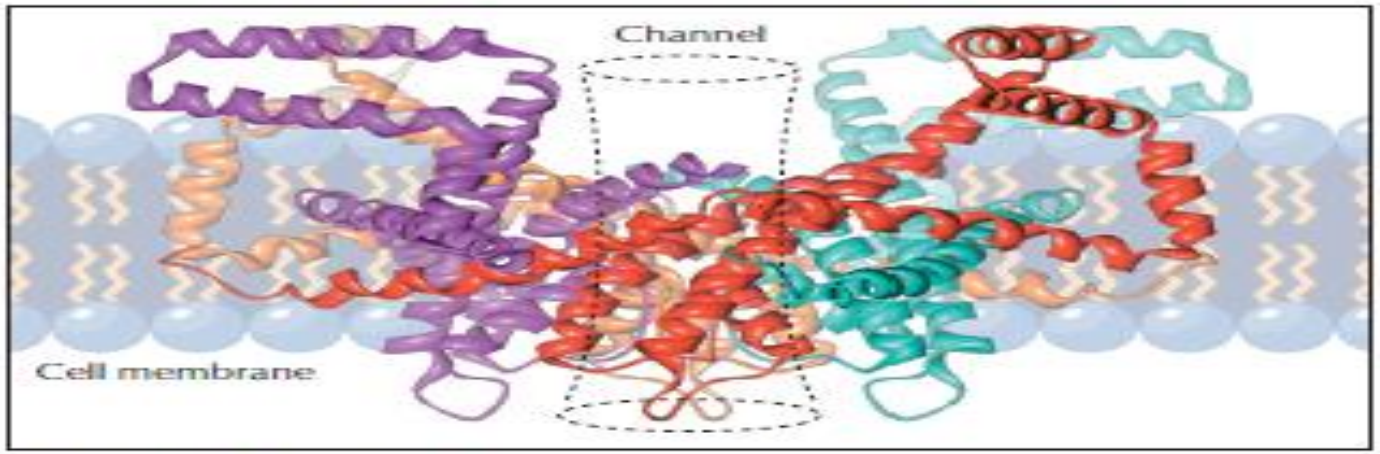
| Class | Drug | Relative Duration of Action |
|---|---|---|
| Amides | Bupivacaine | Long |
| | Lidocaine | Medium |
| | Mepivacaine | Medium |
| | Prilocaine | Medium |
| | Ropivacaine | Long |

| Class | Drug | Relative Duration of Action |
|---|---|---|
| Esters | Benzocaine | Topical only |
| | Cocaine | Medium |
| | Procaine | Short |
| | Tetracaine | Long |

## Voltage-Gated $Na^+$ Channel

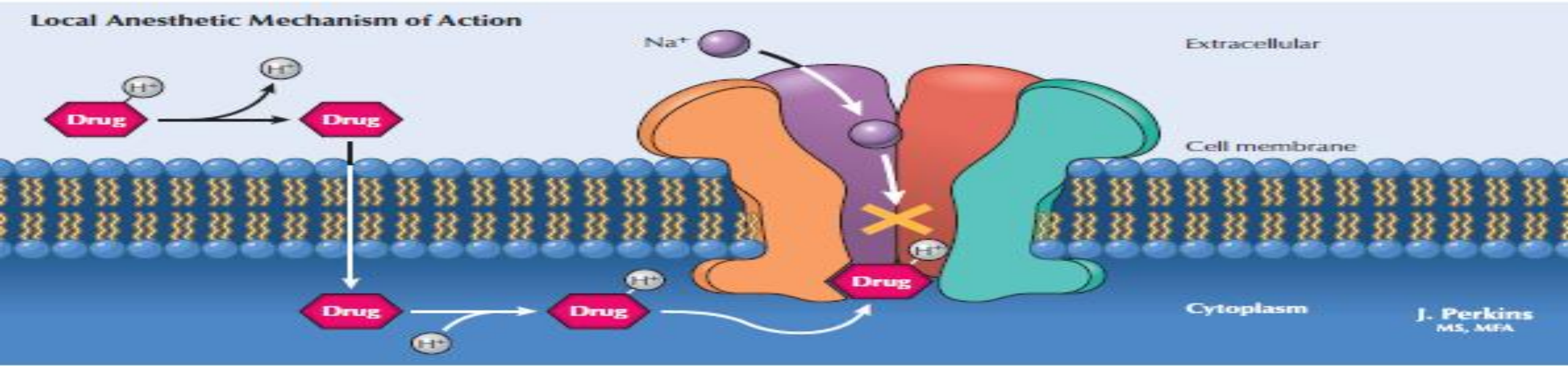



Extracellular ("top") view of $Na^+$ channel




Side view of $Na^+$ channel

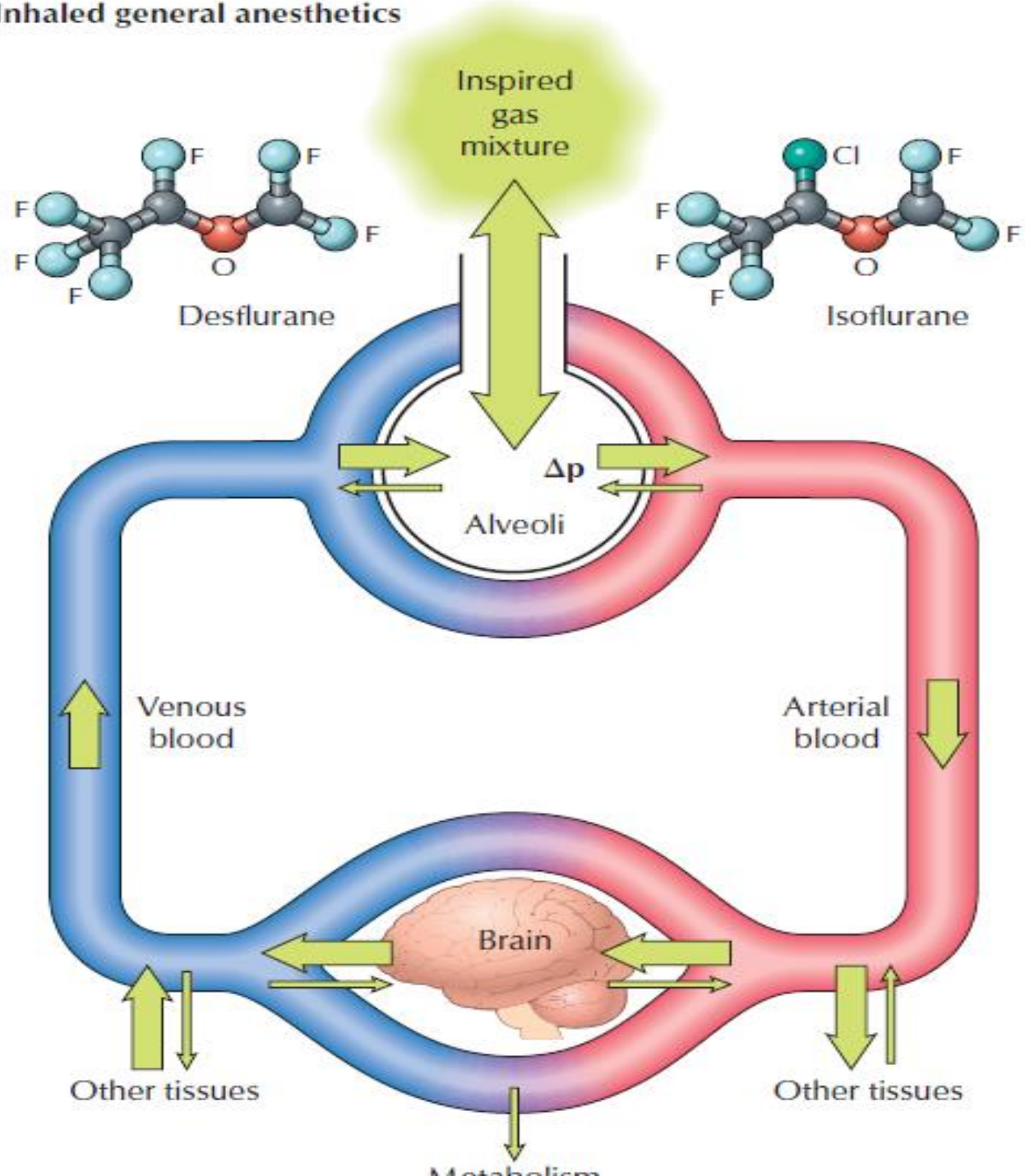
## Local Anesthetic Mechanism of Action



**Selected General Anesthetics**

| Drug Type and Name | Mechanism of Action |
|---|---|
| *Inhalational*<br>Desflurane<br>Enflurane<br>Halothane<br>Isoflurane<br>Methoxyflurane<br>Nitrous oxide<br>Sevoflurane | Not entirely known; postulated to directly activate the $GABA_A$ receptor, leading to enhanced influx of $Cl^-$ and hyperpolarization of neurons |
| *Intravenous*<br>Barbiturates<br>Methohexital<br>Secobarbital<br>Thiamylal<br>Thiopental | Facilitate inhibitory action of GABA at the $GABA_A$ receptor by increasing duration of $Cl^-$ channel opening |
| Benzodiazepines<br>Alprazolam<br>Clonazepam<br>Flurazepam<br>Midazolam | Facilitate inhibitory action of GABA at the $GABA_A$ receptor by increasing frequency of $Cl^-$ channel opening |
| Opioids<br>Alfentanil<br>Fentanyl<br>Morphine<br>Remifentanil | Agonists at opioid receptors widely distributed throughout the central nervous system |
| Phenol<br>Propofol | Not known |
| Dissociative (anesthesia without loss of consciousness)<br>Ketamine | Antagonist at the NMDA (*N*-methyl-D-aspartate) subtype of the excitatory amino acid glutamate receptor |

**Inhaled general anesthetics**



| Adverse Effects | Drug Treatment/Management |
| --- | --- |
| Excessive sedation | Reduce dose by 25% or increase dosing interval |
| Constipation | Casanthranol–docusate one capsule at bedtime or twice daily; senna one to two tablets at bedtime or twice daily; bisacodyl 5–10 mg daily plus docusate 100 mg twice daily; polyethylene glycol 3350 17 grams daily; methylnaltrexone 0.15 mg/kg SQ every other day; naloxegol 12.5–25 mg daily |
| Nausea and vomiting | Prevention: Hydroxyzine 25–100 mg (po/IM) every 4–6 hours as needed; diphenhydramine 25–50 mg (po/IM) every 6 hours as needed; ondansetron 4 mg IV or 16 mg po<br>Treatment: Prochlorperazine 5–10 mg (po/IM) every 3–4 hours as needed or 25 mg PR twice daily; ondansetron 4–8 mg IV every 8 hours as needed |
| Gastroparesis | Metoclopramide 10 mg (po/IV) every 6–8 hours |
| Vertigo | Meclizine 12.5–25 mg po every 6 hours as needed |
| Urticaria/itching | Hydroxyzine 25–100 mg (po/IM) every 4–6 hours as needed; diphenhydramine 25–50 mg (po/IM) every 6 hours as needed |
| Respiratory depression | Mild: Reduce dose by 25%<br>Moderate to severe: Naloxone 0.4–2 mg IV every 2–3 minutes (up to 10 mg) for complete reversal; 0.1–0.2 mg IV every 2–3 minutes until desired reversal for partial reversal; may need to repeat in 1–2 hours depending on narcotic half-life |
| CNS irritability | Discontinue opioid; treat with benzodiazepine |

## Table 34–5

## Selected Adjuvant Analgesics and Suggested Dosing

| Agent | Dosing Guidelines | FDA-Approved Indication |
|---|---|---|
| Amitriptyline (Elavil) | 10–25 mg at bedtime with weekly increments to a target dose of 25–150 mg of amitriptyline or an equivalent dose of another TCA | |
| Duloxetine (Cymbalta) | DPN: 60 mg daily<br>Fibromyalgia: 30 mg daily, may be increased to a target dose of 60 mg/day | DPN, fibromyalgia |
| Gabapentin (Neurontin) | Initially, 300 mg three times a day up to a maximum of 3600 mg daily, in divided doses[a] | PHN |
| Pregabalin (Lyrica) | DPN: Initially, 50 mg three times a day; may be increased to 100 mg three times a day within 1 week based on efficacy and tolerability[a]<br>PHN: Initially 75 mg twice a day or 50 mg three times a day; may be increased to 100 mg three times a day within 1 week based on efficacy and tolerability[a]<br>Fibromyalgia: Initially 75 mg twice a day, increase after 1 week to 300 mg to 450 mg/day (in divided doses every 12 hours) | DPN, PHN, and fibromyalgia |
| Lidocaine 5% (Lidoderm patch) | Up to three patches may be applied directly over the painful site once daily; patches are applied using a regimen of 12 hours on and 12 hours off | PHN |