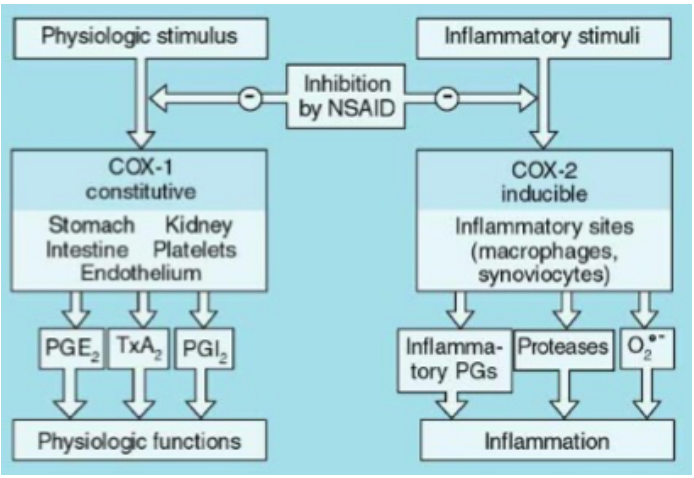
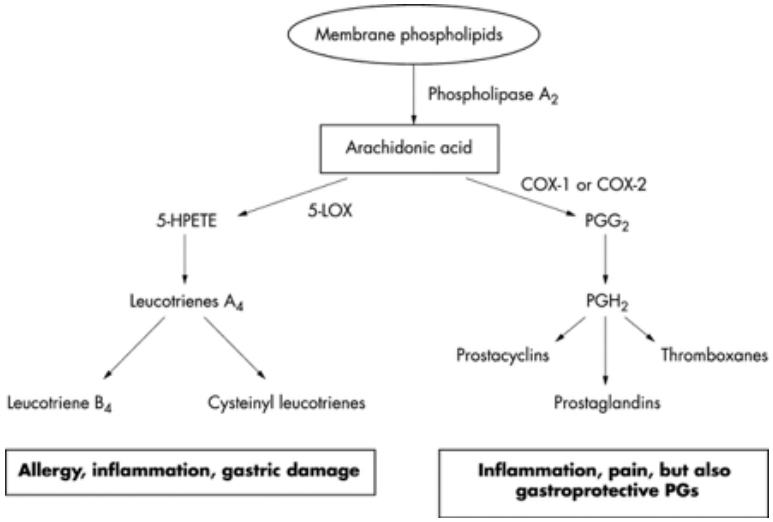
NSAIDs (Ch. 71)

Mechanism of Action





- Ex: Aspirin and ibuprofen
- They work by blocking the active site of the enzymes COX-1 and/or COX-2 depending on if the NSAID is selective or not.
- Damaged cells release arachodonic acid – COX-1 and COX-2 are enzymes that convert it to prostaglandin H2. Those prostaglandins are then converted into other chemicals that cause inflammation and pain. There are active sites on COX-1 and 2 that bind to the prostaglandins that lead to their activation.
- Note: On the top left picture, COX-1 is constitutive - this means that it is always on, it's default state is to be active at any time. COX-2 is inducible - this means it is turned on and off.
- Aspirin works by entering this active site for these molecules and breaks off so it permanently blocks the enzymes (meaning the effect is temporary until these enzymes are recycled).
- Ibuprofen works by entering the active site but it doesn't change the enzyme so its not permanently blocking the enzymes binding site. Eventually ibuprofen can be released from the active site and cox-1 and 2 would be free to bind to other molecules. While the NSAID is bound, the enzyme can't bind prostaglandins–this prevents the pain signalling.

Something to note is that COX-1 and COX-2 enzymes are involved in producing gastroprotective prostaglandins. By blocking COX-1 and 2, we are removing this gastroprotective effect. This is why taking NSAIDS can lead to GI complications such as ulcers.

Hypothesis that anti-inflammatory prostaglandins (PGs) were produced through constitutive expression of COX-1, whereas the proinflammatory PGs were produced via induction of the COX-2 isoform. The traditional NSAIDs were known to inhibit both isoforms of COX and their adverse GI toxicities were attributed to the inhibition of gastroprotective PGs produced via the COX-1 pathway. Shortly thereafter, scientists from the academic community and

pharmaceutical companies focused their efforts on the design of selective COX-2 inhibitors in order to develop superior anti-inflammatory and analgesic agents with reduced adverse effects compared to traditional NSAIDs

COX Inhibitors Classification

There are two generations of NSAIDs that work differently.

- The only NSAID that is used for **prevention of MI and stroke is Aspirin** because it blocks Thromboxane A2 which is a platelet aggregator in the body.
    - No Tx A2 = no platelet aggregation = increased risk of bleeding. None of the other NSAIDS have this property.
- Some of the second generation NSAIDS can increase the risk of MI and stroke.
- **2nd generation** is just as effective as first but has a **lower risk for GI side effects**, but increased risk for MI or stroke

Another thing to note is that acetaminophen is not an NSAID. Acetaminophen does NOT reduce inflammation. It has analgesic and antipyretic properties but it does nothing for inflammation.

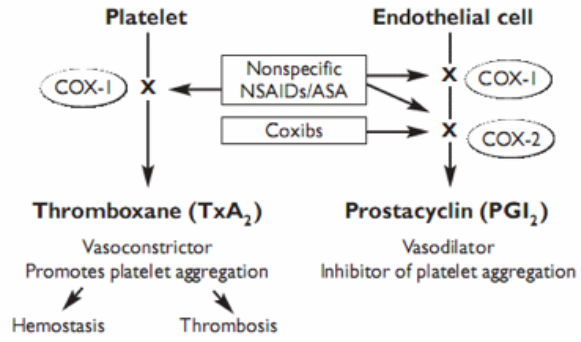
	First-Generation NSAIDs: Aspirin	First-Generation NSAIDs: All Others	Second-Generation NSAIDs (Coxibs)	Acetaminophen
INDICATIONS				
Inflammation	Yes	Yes	Yes	No
Pain	Yes	Yes	Yes	Yes
Fever	Yes	Yes	No	Yes
Prevention of MI and stroke	Yes	No	No	No
ADVERSE EFFECTS				
Gastric ulceration	Yes	Yes	Yes*	No
Renal impairment	Yes	Yes	Yes	No
Bleeding	Yes	Yes	No	No
MI and stroke	No	Yes	Yes	No
Liver damage with overdose	No	No	No	Yes

Studies conclusively demonstrated that selective COX-2 inhibitors may tip the natural balance between prothrombotic thromboxane A2 (TxA2) and antithrombotic prostacyclin (PGI2) potentially increasing the possibility of a thrombotic cardiovascular event - VIOXX

- Platelets do not have a nucleus.
- Irreversible COX-1 inhibition = forever
- Coxibs: decrease vasodilation → increases vasoconstriction

You would think that the blocking of the COX enzymes would cancel out the vasoconstriction and vasodilation and therefore remain the same. This is not true.

- Because platelets do not have a nucleus, they cannot replace the COX enzymes that are



inhibited. The blocking of the thromboxane is going to go on for as long as the platelets live (about 1 week).

- On the other hand, the endothelial cells have a nucleus and can replace the COX enzymes that are being inhibited, so that over a long period of time, the inhibition of prostacyclin will diminish over time so you will have more vasodilation and less platelet aggregation.

Aspirin - General Infos

Irreversible COX inhibitors:

- COX-1 actions: MI & stroke prophylaxis
- COX-2 actions: pain, fever & inflammation
- Adverse effects: gastric ulcers & renal impairment

Pharmacokinetics:

- Excellent oral availability
- 80-90% plasma protein-bound
- Half-life low dose = 2h (1st order) / High dose = 20h (0-order)
- Kidney excretion: alkaline urinary pH increases clearance

Aspirin, also known as **Acetylsalicylic acid,** has been used for thousands of years. It was discovered to be a molecule found in willow tree leaves and bark and gets converted to this active chemical in our bodies – people used to chew them to relieve any discomfort before they even knew how it worked.

Aspirin and ibuprofen are considered to be non-selective COX inhibitors, meaning they bind to both COX-1 and 2. By blocking COX-1, you prevent platelet aggregation and therefore risk of MI and stroke and prevent gastroprotective effects. By blocking COX-2, you reduce fever, pain and inflammation because you're blocking the proinflammatory response. There is a risk of ulcers due to the inhibited gastroprotective effects of COX.

Studies have shown that NSAID-induced sodium retention in healthy and elderly patients is mediated by the inhibition of COX-2, whereas a decreased glomerular filtration rate is associated with inhibition of COX-1. These studies confirm that both COX isoforms are involved in renal physiology.

COX-1–mediates prostaglandins that are involved with protection of the stomach lining
COX-2–mediates prostaglandins responsible for pain and inflammation

Aspirin - Therapeutic Uses

Action	Examples
Anti-Inflammation	**Drug of Choice: Arthritis (Rheumatoid, Osteo, Juvenile)** Other indications: Rheumatic Fever; Tendinitis Required dosage > Analgesia or Antipyretic
Analgesia	**Mild to Moderate Pain** **Best in Joints, Muscles & Headache** / Poor for intense Visceral pain No tolerance/dependence → Safer than Opioids
Antipyretic	Drug of Choice for Adults / **Contraindicated in children!!** Only ↓ Temperature induced by inflammatory pyrogens
Dysmenorrhea	↓ Prostaglandins in Uterus → **↓ Cramps** **Ibuprofen > Aspirin**
Antiplatelet Aggregation	#1 Use of Aspirin Today → **More on that one NEXT WEEK** Recommended if risk/previous history of Strokes or Myocardial Infarcts
Cancer Prevention	**Colorectal Cancer:** Low dose ↓ incidence & mortality via COX-2 Inhibition Mixed evidence for all other solid tumors

Question

You are a nurse working in a community setting and a mother asks if she could give her 2y.o. child aspirin. You reply:

- NO! Used to be given to children if they were sick but it was linked with **REYES SYNDROME**. It affects young children and can cause swelling in the liver and brain. Acetaminophen = better option.

Aspirin Adverse Effects

➔ Most common during long-term anti-inflammatory use
➔ Most are uncommon unless risk factors present

- Gastric ulcers, perforation & bleeding
  - This is due to the blocking of COX-1 enzymes which stimulate the secretion of gastric secretions to form a barrier.
  - Risk factors = age, smoking & alcohol, history of ulcers
  - Prophylaxis: proton pump inhibitor & H2 antagonists
- Bleeding: antiplatelet action
  - Discontinue 1 week before elective surgery
- Acute renal impairment: edema & increased blood urea nitrogen
  - Risk factors = age, hepatic cirrhosis, heart failure, kidney damage
- Salicylism: high levels of salicylic acid in the body
  - Light early signs of aspirin toxicity (ex. tinnitus)
- Reye's syndrome: rare but mortality = 30-40%
  - Link between NSAIDs + chickenpox/influenza in kids → use acetaminophen
- Others: hypersensitivity reactions, teratogen + prolonged labor

Aspirin - Interactions & Poisoning

Significant interactions:

- Anticoagulants: increased antiplatelet effect

- Glucocorticoids: increased risk of gastric ulcers
- Alcohol: increased risk of gastric bleeding
- Other NSAIDs: decreased MI/stroke prophylaxis
- Angiotensin inhibitors: increased renal impairment
- Decreased vaccine effectiveness
    - because these drugs are antiinflammatory, and by preventing the antiinflammatory response you're preventing the effectiveness of the vaccines.

Acute poisoning:

- Acute medical emergency = 20-25g for adults; 4g for children
- Salicylism alkalosis → respiratory depression → acidosis + electrolyte imbalance → coma & death
- Treatment: respiratory support + bicarbonate infusion (to neutralize some of the acid buildup, and hopefully reverse the acidotic state) and discontinue the drug.

<u>Other 1st Gen NSAIDs</u>

- Main difference vs. Aspirin → **reversible COX inhibitors**
- As such:
    - Slightly less renal & GI adverse effects
    - Increased risk of stroke and MI
- All have similar clinical safety & efficacy
- Unexplained individual variations in response & tolerance

Ibuprofen (Advil, Motrin, etc.)

- Greater relief of dysmenorrhea than aspirin
- Decreased risk of GI bleeding & antiplatelet than aspirin

Recent study: ductus arteriosus closure - Indomethacin reduces need for surgery

- Ductus arteriosus is a blood vessel that allows blood to go around the baby's lungs before birth. Soon after the infant is born and the lungs fill with air, the ductus arteriosus is no longer needed. Most often closes a couple days after birth.
- If the vessel doesn't close → Indomethacin (indocin) is an NSAID used to close the patent ductus arteriosus (PDA).
- Indomethacin → blocks the enzyme cyclooxygenase inhibiting prostaglandin synthesis thereby facilitating ductal closure.

<u>2nd Gen NSAIDs: Coxibs</u>

- Theory: COX-2 selective inhibition = decrease pain/fever/inflammation + no GI ulcers
- Reality: only small decrease in GI ulcers & huge increased risk of MI & stroke

- VIOXX scandal: VIOXX was made by Merck as a selective COX-2 inhibitor. It was marketed to treat osteoarthritis, acute pain and period cramps and scientists had really high hopes that it would work. Early on, there was evidence supporting an increased cardiovascular risk but this evidence was ignored/fudged. Data was altered and the drug

was produced. VIOXX rapidly became a blockbuster drug bringing in millions of dollars per year. In 2004, Merck removed the drug from the market because studies showed a huge increase in heart attacks and strokes from patients taking this medication. The data could no longer be ignored – too many adverse events were being reported. It cost Merck hundreds of $ in legal expenses and is one of the most widely used drugs to be pulled from the market.

- Prototype: Celecoxib
    - Proven to have better efficacy and be safer
    - Similar uses & adverse effects as other NSAIDs
    - Extra use: decrease colorectal cancer risks in FAP patients
    - GI ulcers: increased safety at 6 months, disappears at 12 months (risk becomes the same as other NSAIDs)
    - Significant interaction: increases warfarin anticoagulation action
        - monitor closely for risks of bleeding

Question

Your friend went out drinking last night and now has a bad headache. He asks you if he should take Tylenol. You reply:

- NO! Alcohol enhances acetaminophen metabolism into a toxic product, potentially causing liver damage.

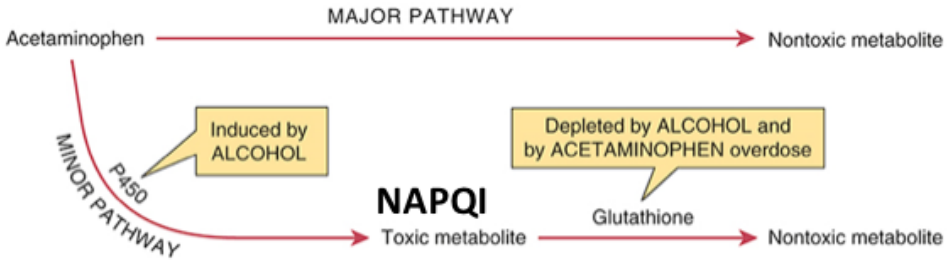
The Black Sheep: Acetaminophen

- Analgesic & antipyretic actions → best option
- No antiinflammatory & antiplatelet effects
- No gastric ulcers, renal impairment & Reye's syndrome
- Hypothesis: CNS-selective COX inhibition
- Potential risk of hypertension with daily intake
- Interactions: increases warfarin action / decreases vaccine power

Acetaminophen mechanism of action:

- It is metabolized in two pathways by the liver.
- The major pathway converts it into a nontoxic metabolite.
- The minor pathway involves the p450 enzymes that convert it into a toxic metabolite called NAPQI. This metabolite is normally neutralized by glutathione.
    - When you drink alcohol and take acetaminophen, the p450 enzymes are induced by alcohol so there's a much greater amount of toxic metabolites in your system.
    - You need a lot of glutathione to neutralize this amount of toxic metabolite. What happens is the body runs out and the toxic metabolite accumulates → causes an overdose. The liver is unable to metabolize both acetaminophen and alcohol, and cell death may result.
- Treatment (antidote) is acetylcysteine which increases the amount of glutathione available so the toxic metabolite is converted into a non-toxic form.

*nb. Glutathione is an antioxidant, an agent that prevents certain highly reactive, oxygen-containing molecules (ie. reactive oxygen species) from damaging the cells.



Acute toxicity: Liver damage
- Overdose + alcohol
- Hepatic necrosis = 48-72h
- Tx: acetylcysteine → increases glutathione
    - Nb. acetylcysteine is the precursor to glutathione

Nursing Capsule: AHA Statement - Chronic Pain & COX Inhibitors
Musculoskeletal pain management in cardiovascular event high risk patients (only move to next step if previous one fails):
- Step 1: non-drug interventions → physical therapy, heat/cold applications, weight loss
- Step 2: acetaminophen or aspirin are preferred (because they have the smallest CVS risk compared to the others)
- Step 3: other non-selective NSAIDs (ex. Naproxen, Ibuprofen)
- Step 4: COX-2 selective inhibitors (ex. Celecoxib)
    - Opioid if pain too intensive
    - This is the last resort because non-selective NSAIDs have a higher risk of CVS events compared to selective NSAIDs

➔ Try the minimum effective dose for the shortest amount of time to reduce risks of toxicity.
➔ For high risk of thrombosis patients: add low-dose aspirin + proton pump inhibitor or H2-antagonist (to reduce risk for GI ulcers)

Headache Medications (Ch. 30)

PATHO REVIEW
Migraine
- Episodic headaches
    - 4-72h at a time
    - With or without aura
    - Women > men
- Common manifestations:
    - Pulsatile pain
    - Nausea/vomiting

    - Photo/phonophobia
- Multifactorial disorder with several comorbidities
    - Includes: GI, pulmonary, CVS, neurological, sleep and psychiatric disorders

Migraine Aura

People suffering from migraines often know when they're going to get one because they see this "aura" - a visual disturbance

Episodic vs. Chronic Migraine

- Chronic migraines: 15 days of migraine/month or 3+ months of episodic migraines
- Prophylactic Tx relieves Sx before start of migraine which is what we want to do

Migraine: Pathophysiology

- Involvement of trigeminal nerves; cortical depression and vasomotor activity
- Clinical phases of a migraine:
    - 1. Premonitory → Sx hours before aura and onset of headache (ex. Neck pain, yawning)
    - 2. Migraine aura (~1h) → cortical spreading depression (CSD) from occipital lobe
        - Visual Sx caused by decreased electrical activity & blood flow to occipital area
    - 3. Headache → several proposed pain mechanisms (see next part)
    - 4. Recovery (several hours)

Proposed Headache Mechanisms

1. Activation of trigeminal cervical afferents
   ↓
   Release of vasoactive peptides + inflammatory mediators → CGRP
   ↓
   Activation of cerebral vessel nociceptors
2. Abnormal processing of trigeminal pain afferent signals at thalamus & primary sensory cortex
3. Central sensitization (allodynia) of the thalamus
4. Dilation of carotid artery terminal branches

Preclinical evidence suggests that, during a migraine, activated primary sensory neurons (meningeal nociceptors) in the trigeminal ganglion release CGRP from their peripherally projecting nerve endings located within the meninges. This CGRP then binds to and activates CGRP receptors located around meningeal vessels, causing vasodilation, mast cell degranulation, and plasma extravasation. Human observations have further implicated the role of CGRP in the pathophysiology of migraine. Activation of primary sensory neurons in the trigeminal vascular system in humans can cause the release of CGRP.

- During some migraine attacks, increased concentrations of CGRP can be found in both saliva and plasma drawn from the external jugular vein.

CGRP (calcitonin gene-related peptide) – produced in central and peripheral neurons. It is a potent vasodilator and functions in the transmission of nociception (aka pain).

Migraine & Estrogen

- Increased estrogen levels (ex. menstruation)
    - Stimulation of trigeminal ganglia
    - Vasoactive regulation at vascular smooth muscles & hypothalamus
- No direct link between estrogen & increased frequency & severity of migraines
    - Only hypothesized to explain sex differences

BACK TO PHARM

Treatment Overview

- Role of CGRP & 5-HT in migraine
    - 1. CGRP levels rise during migraine attack while 5-HT (ie. serotonin) levels drop
    - 2. 5-HT administration can decrease CGRP release
- Theory: decreased CGRP = decreased vasodilation = decreased nociception transmission = decreased pain

The activation of 'trigeminovascular system' causes release of various vasodilators, especially CGRP that induces pain response. At the same time, decreased levels of the neurotransmitter serotonin have been observed in migraineurs. Serotonin receptors have been found on the trigeminal nerve and cranial vessels and their agonists, especially triptans, prove effective in migraine treatment. It has been found that triptans act on trigeminovascular system and bring the elevated serum levels of key molecules like CGRP to normal (increase serotonin, and decrease CGRP).

- Non-pharmacological interventions
    - On a daily basis: healthy exercise, sleeping and diet patterns decrease the intensity and frequency of migraines
    - During migraine attack: relax in dark quiet room + ice pack on neck
- Available medications aim to:
    - 1. Abort ongoing migraines → decrease pain, nausea & vomiting
        - Mild to moderate pain: NSAIDs (non-specific drugs)
        - Moderate to severe pain: 5-HT agonists (migraine-specific drugs)
        - Last resort: opioids
    - 2. Prevent future migraines → anti-epileptic / beta-blockers / tricyclic antidepressants
    - 3. Adjunct drugs: antiemetics (ex. metoclopramide) → can allow PO administration of above drugs.
        - If you are experiencing a migraine and N/V and taking PO pills to stop it without addressing the N/V, you're just going to vomit the medication. Taking an anti-emetic will address the N/V so the other PO medications can be taken.

- Migraine prophylaxis should be considered when one or more of the following are present:
    - 1) recurring migraines that significantly interfere with the patient's daily activities, despite acute treatment
    - 2) frequent headaches
    - 3) failure, overuse, or contraindication of acute treatments
    - 4) adverse effects of acute treatment
    - 5) presence of rare migraine conditions which can potentially cause neurologic damage

A good example of a pre-emptive approach to treatment is the patient who suffers from migraine headaches triggered by sexual activity or by exercise. Can take NSAIDS beforehand. Preventive would be more in general. Preemptive is more time-limited

Nursing Capsule: Medication Overuse Headache (MOH)
*Patient education opportunity: chronic use of headache medication CAN trigger headaches!!

As each dose of medicine wears off, the pain comes back, leading them to take even more. This overuse causes your medicine to stop helping your pain and actually start causing headaches. Medication-overuse headache, in contrast, is a dull constant headache which is often worse in the morning. It is present on most days or part of every day. The need to alleviate these withdrawal symptoms perpetuates further use of painkilling drugs and can result in a cycle of medication overuse.

- Affects all abortive migraine medications
- Rebound headache withdrawal intensity:
    - Triptans (5 HT agonist) = mild
    - Analgesics & ergots = longer + intense
- Prevention:
    - Abortive drug use: < 2-3x/week
    - Alternate between abortive drugs
    - Initiate non-pharmacological & prophylactic measures

Ways to prevent MOH but the treatment is to discontinue the abortive medication.

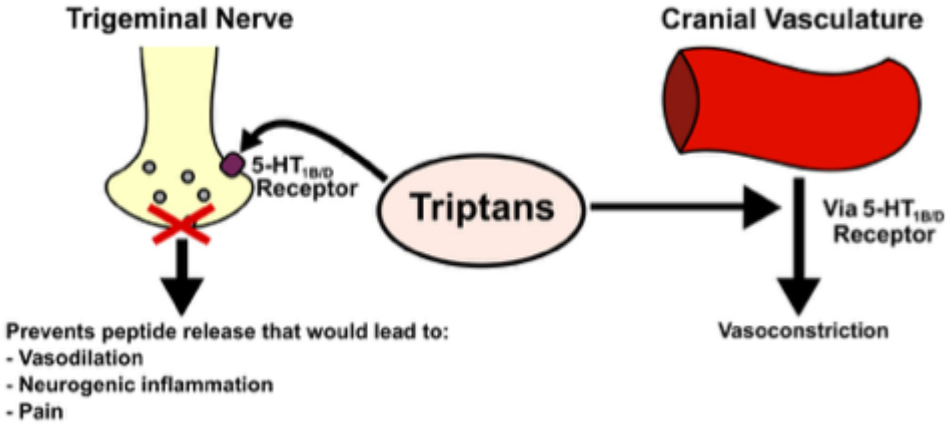
1. Medication-overuse headache (MOH) is a chronic daily headache and a secondary disorder in which acute medications used excessively causes headaches in a headache-prone patient.
2. MOH is clinical diagnosis and a history of analgesic use more than 2-3 days per week in a patient with chronic daily headache is indicative of this diagnosis.
3. MOH most commonly occurs in people with primary headache disorders like migraine, cluster, or tension-type headaches using less effective or nonspecific medications resulting in inadequate treatment response and re-dosing
4. MOH development is linked to baseline frequency of headache days per month, acute medication class ingested, frequency of acute medications ingested, and other risk factors.

5. MOH has been found to render headaches refractory to both pharmacological and non-pharmacological prophylactic medications, and also reduces the efficacy of acute abortive therapy for migraines.
6. The most effective method to treat MOH is discontinuation of the medication that is overused and a combination of pharmacological, non-pharmacological, behavioral and physical therapy interventions.
7. Use of certain classes of acute medications such as opioids, barbiturate-containing analgesics and butalbital, aspirin and caffeine is associated with increased risk of chronic migraine

<u>1. Serotonin 1B/1D Agonists: Sumatriptans</u>

Action:

- Triptans are serotonin (5-HT) agonists with high affinity for 5-HT1B and 5-HT1D receptors.
- Migraine returns ~ 40% of patients
- Uses: relief of all migraine symptoms by causing cranial vasoconstriction, most likely through action at postsynaptic 5-HT1B receptors on the smooth-muscle cells of blood vessels.
- It is also now theorized that triptans also block the release of vasoactive peptides from the perivascular trigeminal neurons through their action at presynaptic 5-HT1D receptors on the nerve terminals.
- In addition, triptans **bind to presynaptic 5-HT1D receptors in the dorsal horn**, and this binding is thought **to block the release of neurotransmitters** that activate second-order neurons ascending to the thalamus. **Triptans may also facilitate descending pain inhibitory systems**.
- Sumatriptan is most effective when taken early at the start of a migraine. It does not prevent future migraines or lessen how often you get migraine attacks - ABORTIVE!



Kinetics:

- PO, Nasal or Subcutaneous administration
- MAO metabolism → half-life = 2.5 hours

Adverse effects:

- Teratogen!!!
- 50% of patients → chest pressure
- Very rare: coronary vasospasms

Interactions:

- Other triptans/Ergot alkaloids → additive effects
- MAO & reuptake inhibitors → increases effects

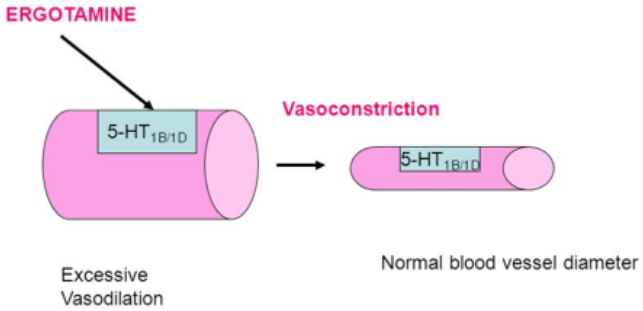
Other Triptans Advantages:

- Naratriptan → delayed onset + long duration
- Rizatriptan → most consistent efficacy
- Almotriptan → chest pressure only in 0.3% patients
- Frovatriptan → lowest rate of migraine return
- Eletriptan → fastest onset

2, Ergot Alkaloids

Ergotamine

- Alpha-adrenergic + DA + 5-HT1B/1D partial agonist
- Mechanism = triptans + other unknown effects
- 2nd line drug for migraine attacks
- It has biological activity as a vasoconstrictor
- Used to treat acute migraines (sometimes with caffeine). The common form of prescription is Cafergot which is a combination of caffeine and ergotamine.
- Derived from a fungus ergot
- Mechanism of action is complex: The molecule shares structural similarity with neurotransmitters such as serotonin, dopamine, and epinephrine and can thus bind to several receptors acting as an agonist. The anti-migraine effect is due to constriction of the intracranial extracerebral blood vessels through the 5-HT1B receptor, and by inhibiting trigeminal neurotransmission by 5-HT1D receptors. Ergotamine also has effects on the dopamine and norepinephrine receptors. Its side effects are due mainly to its action at the D2 dopamine and 5HT1A receptors



Kinetics:

- PO, sublingual or rectal administration
- CYP3A4 metabolism → half-life = 2 hours
- Effects observed more than 24h post-administration

Adverse effects:

- Increased nausea and vomiting = 10% of patients
- Known teratogen
- Increased physical dependence

Interactions:

- Triptans/other ergot alkaloids → additive effects
- CYP3A4 inhibitors → increased toxicity → ERGOTISM
    - if you are taking another drug that is a CYP3A4 inhibitor, you are not metabolizing the ergotamine and there is an increased toxicity that leads to ergotism.

Dihydroergotamine

Advantages:

- Same mechanism & efficacy
- No nausea & physical dependence
- Decreased peripheral vasoconstriction

Drawbacks:

- Prominent diarrhea
- Parenteral & nasal spray only

History Capsule: Ergotism & Witches

- Ergotism is caused by a fungus that affects rye, wheat and other cereal grasses. When first infected, the flowering head of a grain will spew out sweet, yellow-colored mucus, called “honey dew,” which contains fungal spores that can spread the disease. Within them are potent chemicals: ergot alkaloids, including lysergic acid (from which LSD is made) and ergotamine (now used to treat migraine headaches).
- The alkaloids affect the central nervous system and cause the contraction of smooth muscle — the muscles that make up the walls of veins and arteries, as well as the internal organs.
- Toxicologists now know that eating ergot-contaminated food can lead to a convulsive disorder characterized by **violent muscle spasms, vomiting, delusions, hallucinations, crawling sensations on the skin**, and a host of other symptoms.
- Ergot thrives in warm, damp, rainy springs and summers. Those exact conditions had been present in 1691. Nearly all of the accusers lived in the western section of Salem village, a region of swampy meadows that would have been prime breeding ground for the fungus.
- At that time, rye was the staple grain of Salem. The rye crop consumed in the winter of 1691-1692 — when the first unusual symptoms began to be reported — could easily have been contaminated by large quantities of ergot. The summer of 1692, however, was dry, which could explain the abrupt end of the “bewitchments.” Still a hypothesis…

3. Analgesics

NSAIDs

- Aspirin + metoclopramide (antiemetic)
- Efficacy = Sumatriptan
- Less expensive and less adverse effects < Sumatriptan
- Excedrin is also used for migraines and consists of acetaminophen, aspirin and caffeine.
- Other NSAIDs: diclofenac/naproxen

Opioids

- Only severe migraines when other Tx failed
- Butorphanol nasal spray = preferred
    - CNS effects: sedation & dizziness
    - N/V are common
    - Increased perspiration is often experienced
- Meperidine = 2nd choice (increased adverse effects)

Preventive Agents

- Goal = decrease intensity + frequency + duration
- Indications = chronic migraines / severe migraines / failure of abortive drugs

Migraine headache: drugs for preventive therapy:

- **Beta-adrenergic blocking agents** (best prophylaxis option - effective > 70% of patients)
    - Metoprolol
    - Propranolol → interacts with 5HT receptors and inhibits production of NO.
- **Antiepileptic drugs** (only decrease frequency - cost & adverse effects > beta blockers)
    - Divalproex
    - Topiramate
- **Tricyclic antidepressants** (benefits = propranolol - cardiac adverse effects)
    - Amitriptyline
- **Estrogens** (for menstrual associated migraines +/- 2 days of menses - triptans can also help)
    - Estrogen gel
    - Estrogen patch

ANTIHISTAMINES (Ch. 70)

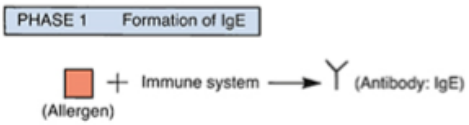
Histamine

Histamine is a compound involved in:

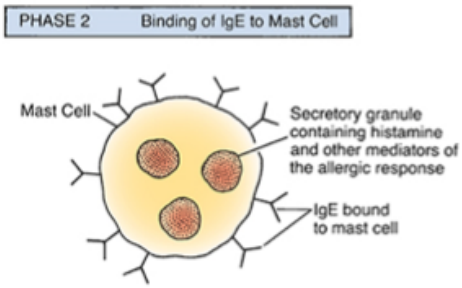
- immune responses
- regulating physiological function in the gut
- acting as a neurotransmitter for the brain, spinal cord, and uterus
- involved in the inflammatory response, and it is made by basophils and mast cells.

Clinical significance:

- Mild allergic responses
- Peptic ulcers

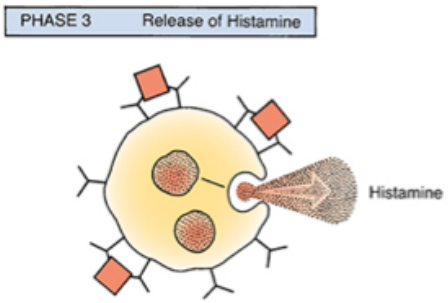


Histamine mainly increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues



Most histamine in the body is made in granules in mast cells and in white blood cells (leukocytes) called basophils. Mast cells are especially numerous at sites of potential injury — the nose, mouth, and feet, internal body surfaces, and blood vessels.

We are interested in histamine release in an immunological context. Mast cells and basophil cells, if sensitized by IgE antibodies attached to their membranes, degranulate when exposed to the appropriate antigen.



So in summary, an allergen (such as pollen) makes the immune system make IgE antibodies. IgE antibodies bind to mast cells. This causes the mast cells to degranulate, or release histamine.. Histamine binds to H1 and H2 receptors. H1 receptor activation causes those potential effects listed. H2 receptors on the other hand cause gastric acid secretion.

Storage/synthesis

- Mast cells → GI, lungs, skin, CNS neurons

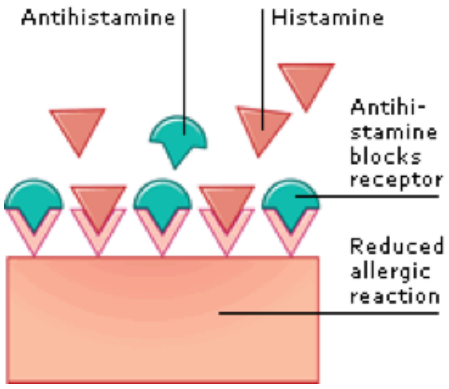
Histamine receptor effects:

- H1-receptors:
  - Vasodilation
  - Increased capillary permeability → edema
  - Bronchoconstriction (exogenous histamine only)
  - Cognition, memory, & sleep cycle
  - Pain, itching, and mucous secretions
- H2-receptors:
  - Gastric acid secretion

H1-Antagonists Pharmacology

Actions:

- Block histamine action (not release!) at the H1 receptor which is caused by IgE binding to mast cells
- Some are also muscarinic blockers
    - This lack of receptor specificity is why some first H1 receptor blockers have poor tolerance.
- Periphery: decreased pain, edema and mucous secretions
- CNS: 1st gen = sedation!! vs. 2nd gen = non-sedative
    - 1st gen has a greater range of side effects due to its lack of receptor specificity (ex. Benadryl/Diphenhydramine)
    - 2nd gen is more selective to peripheral H1 receptors, so it has reduced side effects (ex. Loratidine/Claritin)
- Sedation tolerance develops within days
- toxicity/overdose = CNS stimulation → convulsions
- Large margin safety



Therapeutic Uses:

- Mild allergic responses → hay fever, acute urticaria
- Anti-motion sickness effects: decreases nausea and vomiting
- Insomnia → via CNS sedation
- Fun fact: OTC insomnia meds = ineffective dose

Adverse effects:

- GI effects: nausea, constipation, diarrhea
- Elderly patients: dizziness and confusion
- Anticholinergic effects: dry mouth and increased bronchial mucus
- Interactions: alcohol and CNS depressants
- Caution with pregnancy and breastfeeding

H1-Antagonists Preparations

1st Gen agents:

- Promethazine: avoid if possible because it has profound anticholinergic effects in the elderly.
- Alkylamine: least sedation
- Advantage over 2ng gen: cost

Pharmacologic Effects of H_1 Antagonists Used for Systemic Therapy

Drug	H_1-Blocking Activity[a]	Sedative Effects[a]	Anticholinergic Effects[a]
FIRST-GENERATION AGENTS			
Alkylamines			
Brompheniramine	+ + +	+	+ +
Chlorpheniramine	+ +	+	+ +
Dexchlorpheniramine	+ + +	+	+ +
Ethanolamines			
Clemastine	+ to + +	+ +	+ + +
Diphenhydramine	+ to + +	+ + +	+ + +
Phenothiazines			
Promethazine[b]	+ + +	+ + +	+ + +
Piperazines			
Hydroxyzine	+ + to + + +	+ + +	+ +
Piperidines			
Cyproheptadine	+ +	+	+ +

2nd Gen agents:

- Similar efficacy & safety → choose cheapest
- Low CNS distribution - crosses the BBB at a lower rate because they are very polar
- Fexofenadine: best efficacy/safety ratio
- Interaction with some fruit juices

SECOND-GENERATION (NONSEDATING) AGENTS			
Cetirizine[c]	+ + +	+	±
Levocetirizine[c]	+ + +	+	±
Fexofenadine	+ + +	±	±
Loratadine	+ + to + + +	±	±
Desloratadine	+ + to + + +	±	±

[a] ±, Low to none; +, low; ++, moderate; + + +, high.

[b] Promethazine is contraindicated in children younger than 2 years owing to a risk of fatal respiratory depression. *Parenteral* promethazine can cause severe local tissue injury.

LAXATIVES (Ch. 79)

PATHO REVIEW

Terminus: Large intestine

Remember from pathophys, the large intestine is the last part of the GIT. Water is absorbed here and the remaining waste material is stored as feces and removed by defecation.
There are no villi in the large intestine, they are only in the small intestine. They increase surface area for better absorption of nutrients.

Colon

There are 3 states.

1. One is the irregular rhythm of contraction, which is baseline rhythm.
2. Then there's the **gastrocolic reflex** → gastric secretions increase colon motility
3. Finally there's the **defecation reflex**, which feces (the leftover of what cannot be absorbed) in the rectum goes into the internal anal sphincter

Constipation

- Infrequent/difficult defecation
    - Significant only if quality of life or health decrease
    - Frequency varies → look for individualized decrease in frequency (normal BM frequency is 3x/day to 3x/week)
- Common manifestation = rectal pain & bleeding, anal fissures, hemorrhoids
- Functional constipation = normal rate but difficult evacuation
    - Risk factors = sedentary lifestyle, dehydration, fiber-poor diet, increased emptying suppression
- Slow transit constipation = impaired colon motility or stool block
- Pelvic constipation = decreased pelvic muscle strength or anal sphincter relaxation
- Secondary constipation = complication of disorders or treatments
    - Ex. opioids, neurogenic or endocrine disorders (Parkinson's, diabetes), pregnancy, aging

BACK TO PHARM

General Considerations

Vocab:

- Laxative effect = slow production of soft stool
- Catharsis = prompt/accelerates evacuation of bowels
    - May be an effective means of ridding the lower GI tract of toxins. However, they carry a risk of electrolyte imbalances and dehydration, so they should be used cautiously.

Healthy Bowel Function:

- Fluid reabsorption for soft-but-formed stool
- Frequency of evacuation = large individual variations
- 20-60g dietary fibers daily → optimize bowel function

Constipation:

- Diagnostic: stool hardness > infrequent evacuation
- Best treatment: increase fluid and fiber intake
- Good adjuncts: mild exercises & laxatives (group III)

Other Laxatives Applications:

- Anti-helmintic (parasites) therapy adjuncts
- Pre-surgery bowel emptying (group I)
- Removing ingested poisons

Laxatives Contraindications:

- Any GI inflammation/injuries
- Long-term management of constipation
- Caution during pregnancy/breast-feeding

Bulk-Forming Laxatives

Examples	Psyllium / Methylcellulose (Group III)
Actions	≈ Dietary Fibers Non-digestable or absorbable Colon stretch → ↑ Peristalsis
Indications	Best for Constipation Irritable Bowel Syndrome (IBS) & Diverticulosis
Adverse Effects	No absorption = No Systemic Effects May exacerbate existing intestinal obstruction Esophageal Obstruction if insufficient Fluid with intake

- Psyllium is mainly used as a dietary fiber, which is not absorbed by the small intestine. It is used to relieve the symptoms of both constipation and mild diarrhea.
- The purely mechanical action of psyllium mucilage is to absorb excess water while stimulating normal bowel elimination/softening the stool.
- Psyllium can cause bowel obstructions and bloating. Choking is a hazard if psyllium is taken without adequate water as it thickens in the throat
    - ***Remind patients to take with a full glass of water/juice

Stimulant Laxatives

Examples	Bisacodyl; Senna (Group II) Castor Oil (Group I)
Actions	Stimulate Peristalsis Inhibit intestinal absorption & ↑ GI Secretions
Indications	Opioid-Induced Constipation Slow-Transit Constipation
Adverse Effects	Frequently Abused

- Works by stimulating enteric nerves to cause colonic contractions.
- It is also a contact laxative; it increases fluid and salt secretion
- Castor Oil has a fast action, acts on the small intestine and is too powerful for constipation management.
- Bisacodyl suppository can act in 15 min!

Osmotic Laxatives

Examples	Magnesium or Sodium Salts / Polyethylene Glycol (PEG)
Actions	Poorly Absorbed Salts → Osmotic Pull of Water Stretching of Intestinal Wall → ↑ Motility Low-Dose = Group II vs. High-Dose = Group I
Indications	Poison or Parasite Purge/Evacuation Pre-Surgery Emptying
Adverse Effects	Dehydration Kidney Impairment → ↑ Magnesium Imbalances Sodium Imbalances → ↑ Heart Condition

- PEG is an osmotically acting laxative, that is an inert substance that passes through the gut without being absorbed into the body.
- It relieves constipation because it causes water to be retained in the bowel instead of being absorbed into the body. This increases the water content and volume of the stools in the bowel, making them softer and easier to pass, as well as improving gut motility.

More Laxatives

Surfactant Laxatives	**Docusate Sodium or Calcium (Group III)**
Actions	↓ Feces Surface Tension → ↑ Water Penetration + Inhibit intestinal absorption & ↑ GI Secretions
Other Laxatives	**Lubiprostone (Group III)**
Actions	Chloride Channel Activator ↑ Intestinal Secretions & Motility
Indications	Chronic Idiopathic Constipation IBS with Constipation in women Opioid-Induced Constipation
Adverse Effects	GI Distress (Nausea & Vomiting) & Headaches Rare: Chest Pain + Difficulty Breathing

- Lubiprostone is a fatty acid that acts by specifically activating chloride channels on gastrointestinal epithelial cells, producing a chloride-rich fluid secretion. These secretions soften the stool, increase motility, and promote spontaneous bowel movements.

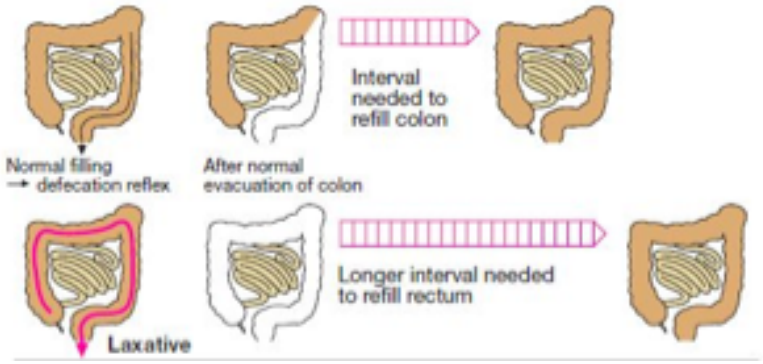
Colonoscopy Bowel Cleansing

Bowel Cleansers	**Infos**
PEG+Electrolyte Solution	**Safest option**: Isotonic → No dehydration or electrolyte imblance **Drawback**: Requires significant fluid intake
Sodium Phosphate	Discussed under osmotic laxatives **Advantage** over PEG: Easier Administration **Drawback**: Hypertonic → Dehydration/Electrolyte Imbalances
Salt Combination	Stimulant + Osmotic Laxatives **Advantage** over PEG: ↑ Cleansing Efficacy **Drawback**: Same as Sodium Phosphate

Nursing Capsule: Laxative Abuse

Causes:

- False belief of mandatory daily bowel movement + aggressive OTC laxative marketing
- Bowel emptying inhibits evacuation until ~ 2-5 days later → misdiagnosed as constipation



Consequences:

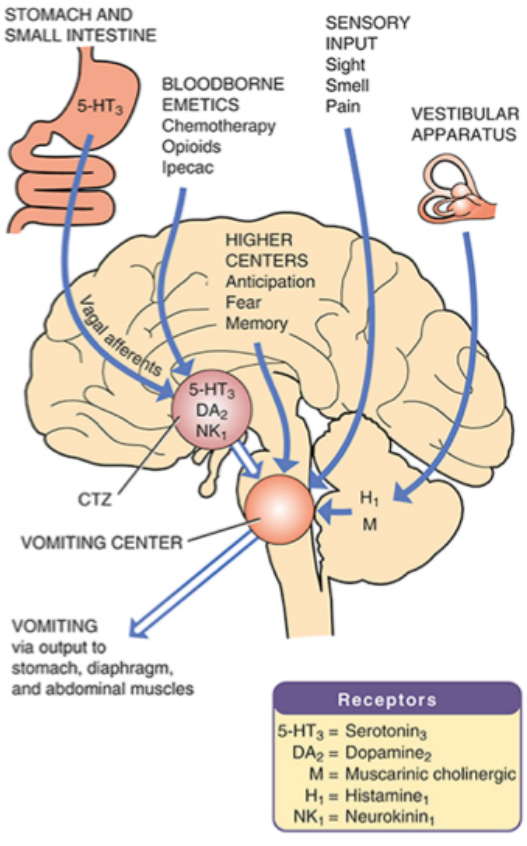
- Inhibition of normal defecation reflex → dependence on laxatives
- Dehydration, electrolyte imbalances, colitis

Treatment:

- Abrupt laxative discontinuation
- Patient education: anticipate few days without evacuation/stool quality > daily movement
- Suggest dietary fiber + daily exercises
- If laxative used again: short-term + lowest effective dose

ANTIEMETICS (beginning of Ch. 80)

- An antiemetic is a drug that is effective against vomiting and nausea.
- Typically used to treat motion sickness and the side effects of opioid analgesics, general anesthetics, and chemotherapy directed against cancer.



Emetic Response

Vomiting (pathophys review)

- Vomiting center in medulla = regulator
- Preceded by nausea & GI muscular events → parasympathetic control
- Nausea = tachycardia + hypersalivation before vomiting → subjective experience

Muscular events:

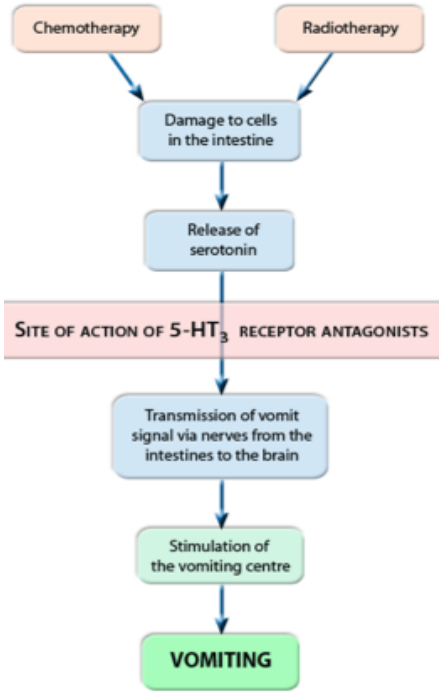
1. Duodenal + gastric retrograde peristalsis
2. LES relaxes + diaphragm & abdominal contraction
3. Increase in thoracic pressure force open UES → chyme expulsion
   Retching = muscular events without fluid expulsion

- Excessive vomiting → fluid, electrolyte & acid-base disorders
- Direct stimulation (increased ICP, tumor, lesion) → projectile vomiting

- Indirect stimulation → anxiety/pain, vestibular system, 5-HT or CTZ stimulation
- CTZ = chemoreceptor trigger zone → outside BBB → drug/toxins

Serotonin Antagonists

Examples	**Ondansetron / Dolasetron / Granisetron**
Actions	5-HT3 Antagonists at CTZ & GI Afferent Neurons
Indications	Chemotherapy-Induced Nausea & Vomiting (CINV) Nausea/Vomiting from Radiotherapy & Anesthesia
Adverse Effects	Headache / Diarrhea / Dizziness **Prolong QT interval**



- These drugs act by blocking serotonin from binding to the 5-HT3 receptor
- Most common is Ondansetron (Zofran) - used to prevent nausea and vomiting in chemotherapy and post-op pts
- Use of ondansetron has been associated with prolongation of the QT interval, which can lead to the potentially fatal heart rhythm known as torsades de pointes → abnormal heart rhythm that can cause sudden cardiac death.
    - So if the MD orders a huge IV dose of Ondansetron, you need to question it and see if the pt has any known cardiac Hx or get a baseline EKG
- Ondansetron is a highly specific and selective serotonin 5-HT_3 receptor antagonist. Serotonin is released by cells in the small intestine in response to chemotherapeutic agents and may stimulate vagal afferents (via 5-HT_3 receptors) to initiate the vomiting reflex.
- Palonosetron is a 5-HT3 antagonist, used to delay emetic response b/c it has a longer half-life (~ 40h)

Other Antiemetic Agents

Antiemetic Drugs: Uses and Mechanism of Action

Class	Prototype	Antiemetic Use	Mechanism of Antiemetic Action
Serotonin antagonists	Ondansetron [Zofran, Zuplenz]	Chemotherapy, radiation, postoperative	Block serotonin receptors on vagal afferents and in the CTZ
Glucocorticoids	Dexamethasone (generic only)	Chemotherapy	Unknown
Substance P/neurokinin$_1$ antagonists	Aprepitant [Emend]	Chemotherapy	Block receptors for substance P/neurokinin$_1$ in the brain
Dopamine antagonists	Prochlorperazine (generic only)	Chemotherapy, postoperative, general	Block dopamine receptors in the CTZ
Cannabinoids	Dronabinol [Marinol]	Chemotherapy	Unknown, but probably activate cannabinoid receptors associated with the vomiting center

- Most effective combination for chemo induced N/V: Serotonin antagonists + glucocorticoids
- CTZ: chemoreceptor trigger zone (CTZ) is an area of the medulla (in the brainstem) that receives inputs from blood-borne drugs or hormones, and communicates with other structures in the vomiting center to initiate vomiting.

- Extrapyramidal symptoms(EPS), also known as extrapyramidal side effects (EPSE), are drug-induced movement disorders that include acute and tardive symptoms.
    - Sx: dystonia (continuous spasms and muscle contractions), akathisia (motor restlessness), parkinsonism (characteristic symptoms such as rigidity), bradykinesia (slowness of movement), tremor, and tardive dyskinesia (irregular, jerky movements).
- Cannabinoids are 2nd line drugs if other antiemetics are not well tolerated
    - 2nd line drugs
    - Anticipate increased use

Drugs for Motion Sickness

Anticholinergics	Scopolamine [Transderm Scōp]	Motion sickness	Block muscarinic receptors in the pathway from the inner ear to the vomiting center
Antihistamines	Dimenhydrinate (generic only)	Motion sickness	Block H_1 receptors and muscarinic receptors in the pathway from the inner ear to the vomiting center

- Scopolamine:
    - Used for motion sickness and post-op nausea/vomiting. Sometimes also used pre-op to decrease saliva.
    - Can be given IV, SubQ, PO or skin patch
    - Usually referred to as a nonspecific anti-muscarinic
    - Most effective
    - Less toxicity with transdermal patch
    - Common ADE = drowsiness
    - Other side effects: dry mouth, blurred vision, headache, urinary retention, and dizziness can occur even at a low dose used in the transdermal patch
    - Overdose: tachycardia, dilated pupils, toxic psychosis, confusion, vivid hallucinations, seizures or coma
- Antihistamines:
    - See H1-blockers discussed earlier
    - Less effective vs. scopolamine + sedation effects = 2nd choice

Nursing Capsule: Chemotherapy & Pregnancy Nausea

Chemotherapy:

- Severe nausea & vomiting → fluid/electrolyte imbalances → patients discontinue treatment
- 3 types of chemotherapy-induced emesis
    - Anticipatory = memory from previous treatment emesis
    - Acute = minutes to 1 day post treatment
    - Delayed = >1 day post treatment
- Treatment: antiemetics most effective for prevention
    - Administer before chemotherapy

Nausea and Vomiting of Pregnancy (NVP)

- 75% of pregnant women during 1st trimester
- 90% resolves before week 20
- Treatments:
    - Non-drug measures = small portions / avoid fatty & spicy foods

- Drug regimen: best & safest option = **doxylamine + vitamin B6 combination** (Diclectin/Diclegis)
  - Doxylamine is an antihistamine & drug combination of pyridoxine/doxylamine
  - Metoclopramide, ondansetron & methylprednisone = last resorts