WASHINGTON STATE UNIVERSITY
Elson S. Floyd
College of Medicine

APPROACHING PHARMACOLOGY

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APPROACHES TO LEARNING PHARMACOLOGY

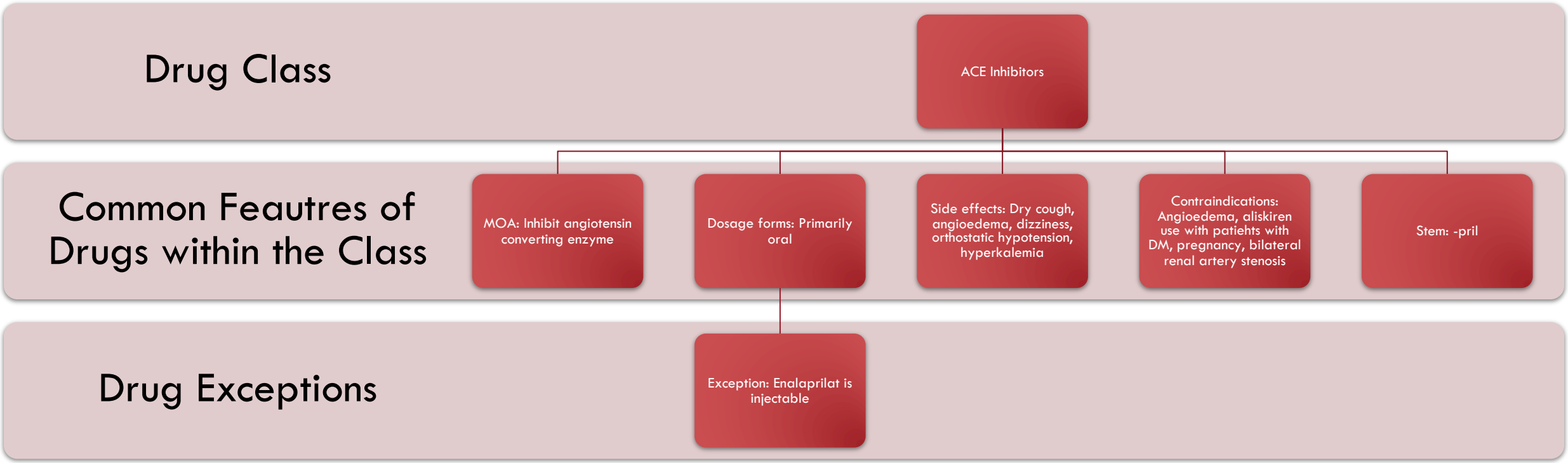
Learn drugs by their class

1. The mechanism of action for the class of drug.
2. Properties or effects that are common to all drugs in the class.
3. Is (are) the drug(s) the drug of choice for some disorder or symptom?
4. Name recognition—what drugs are in this class? Look for common drug stems.
5. Unique features about single drugs in the class.
6. Are there any side effects (rare or not) that may be fatal?

APPROACHES TO LEARNING PHARMACOLOGY

7. Drug interactions.
8. Rare side effects or actions that are common to all drugs in the class.
9. Rare side effects or actions for single drugs in the class.
10. Percentage of drug that is metabolized versus renal excretion.
11. Half-life of each drug in the class.
12. Teratogenicity of each drug in the class.
13. Structure of each drug in the class.

EXAMPLE


Drug Class
ACE Inhibitors
Common Feautres of Drugs within the Class
MOA: Inhibit angiotensin converting enzyme
Dosage forms: Primarily oral
Side effects: Dry cough, angioedema, dizziness, orthostatic hypotension, hyperkalemia
Contraindications: Angioedema, aliskiren use with patiehts with DM, pregnancy, bilateral renal artery stenosis
Stem: -pril
Drug Exceptions
Exception: Enalaprilat is injectable

What is your best studying tip?

GENERAL STUDY TIPS

Utilize matrixes

Spacing versus massing

Interleaving versus blocking

Self-testing

Growth mindset versus fixed mindset

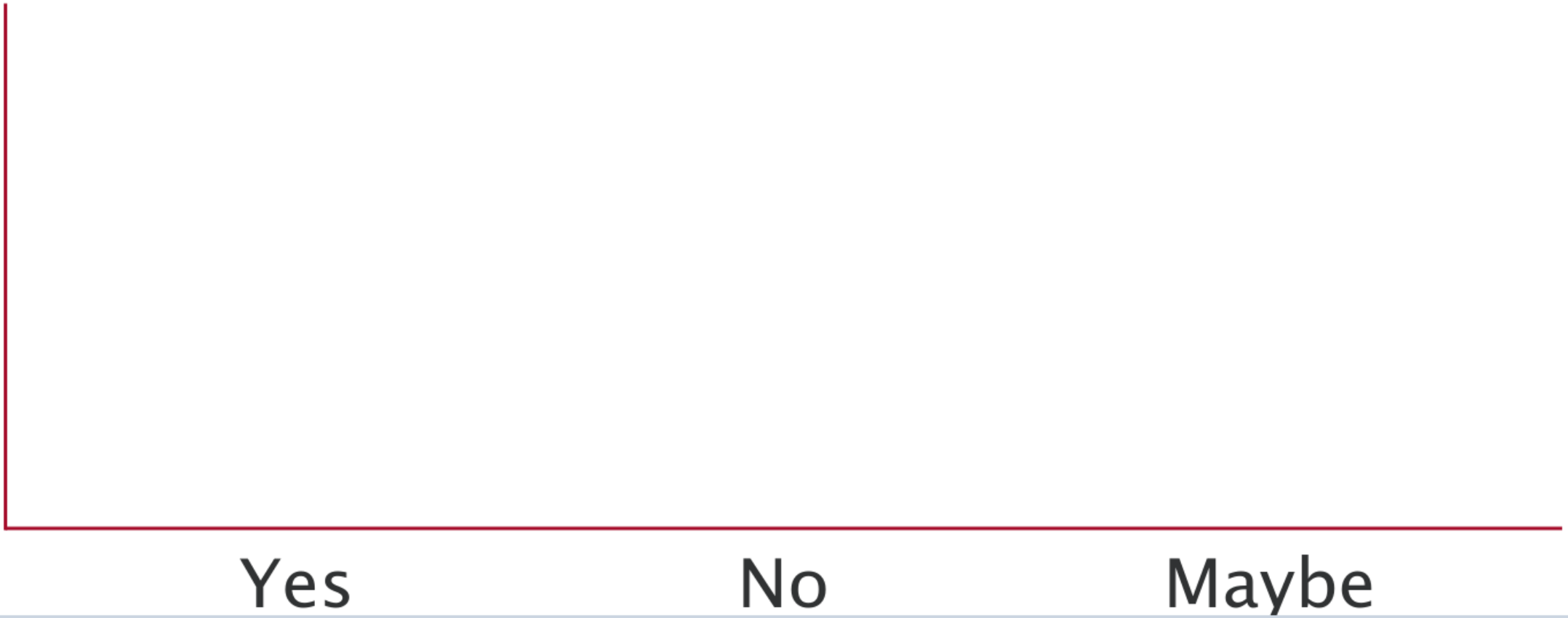
Contiguity Principle

MATRIX EXAMPLE

Matrix 1 Organized topics, organized categories

	Tiger	Lion	Jaguar	Leopard	Cheetah	Bobcat
Call	Roar	Roar	Growl	Growl	Purr	Purr
Weight	Heavy	Heavy	Moderate	Moderate	Light	Light
Life span	Long	Long	Medium	Medium	Short	Short
Habitat	Jungle	Plains	Jungle	Jungle	Plains	Forest
Social behavior	Solitary	Group	Solitary	Solitary	Group	Solitary
Range	Confined	Vast	Confined	Confined	Vast	Confined

Would you be interested in a culinary medicine elective course?



If you answered yes or maybe, which term would you prefer?

PHARMACOLOGY

Anti-inflammatories

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DISCLOSURE

None

Use Statement

OBJECTIVES

1. Describe the common therapeutic uses of aspirin (ASA), non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors
2. Explain the mechanism of action of aspirin, non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors and correlate with underlying pathophysiology
3. Describe and diagram the specific location in the inflammatory cascade where aspirin (ASA), non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors act
4. Describe adverse effects and contraindications to aspirin (ASA), non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors

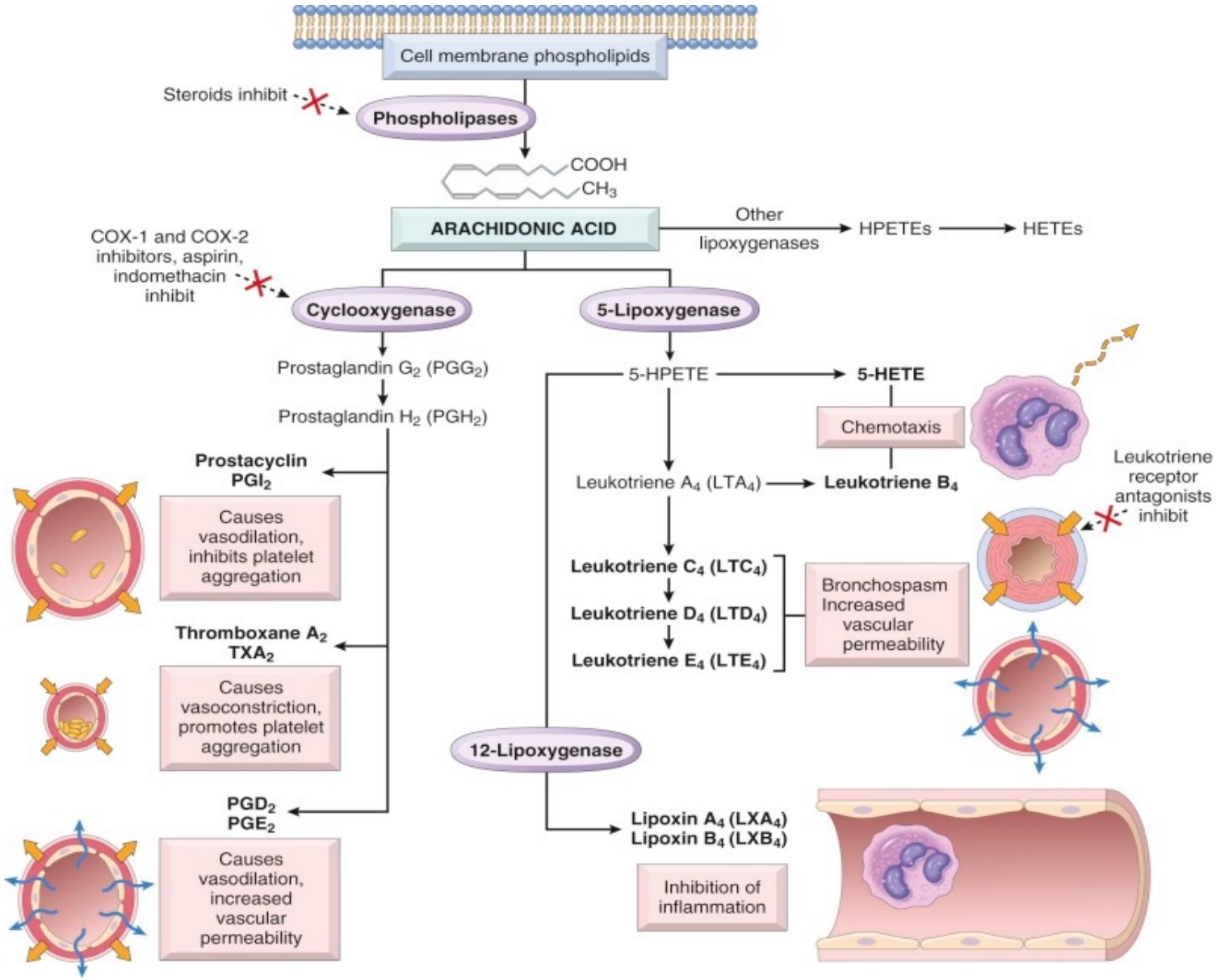
THE CASE OF SK

SK is a 23-year-old female medical student that stumbles down the stairs in MedSci (she claims she wasn't paying attention because she was so energetic, inspired, and enthused after her Wednesday morning CBL session). SK diagnoses herself with a grade I lateral ankle ligament sprain and she has pain and swelling. SK has no other medical conditions, takes only a multivitamin daily, and has an allergy to sulfa drugs (hives).

List inflammatory mediators that could be responsible for SK's pain and swelling.

List inflammatory mediators that could be responsible for SK's pain and swelling.

ARACHIDONIC ACID PATHWAY (INFLAMMATORY CASCADE)



COX-1 AND COX-2 GENERALIZATIONS

COX-1

Relatively constant (constitutive)

Responsible for prostaglandins associated with normal physiologic function

Found in tissues such as stomach, kidney, and platelets

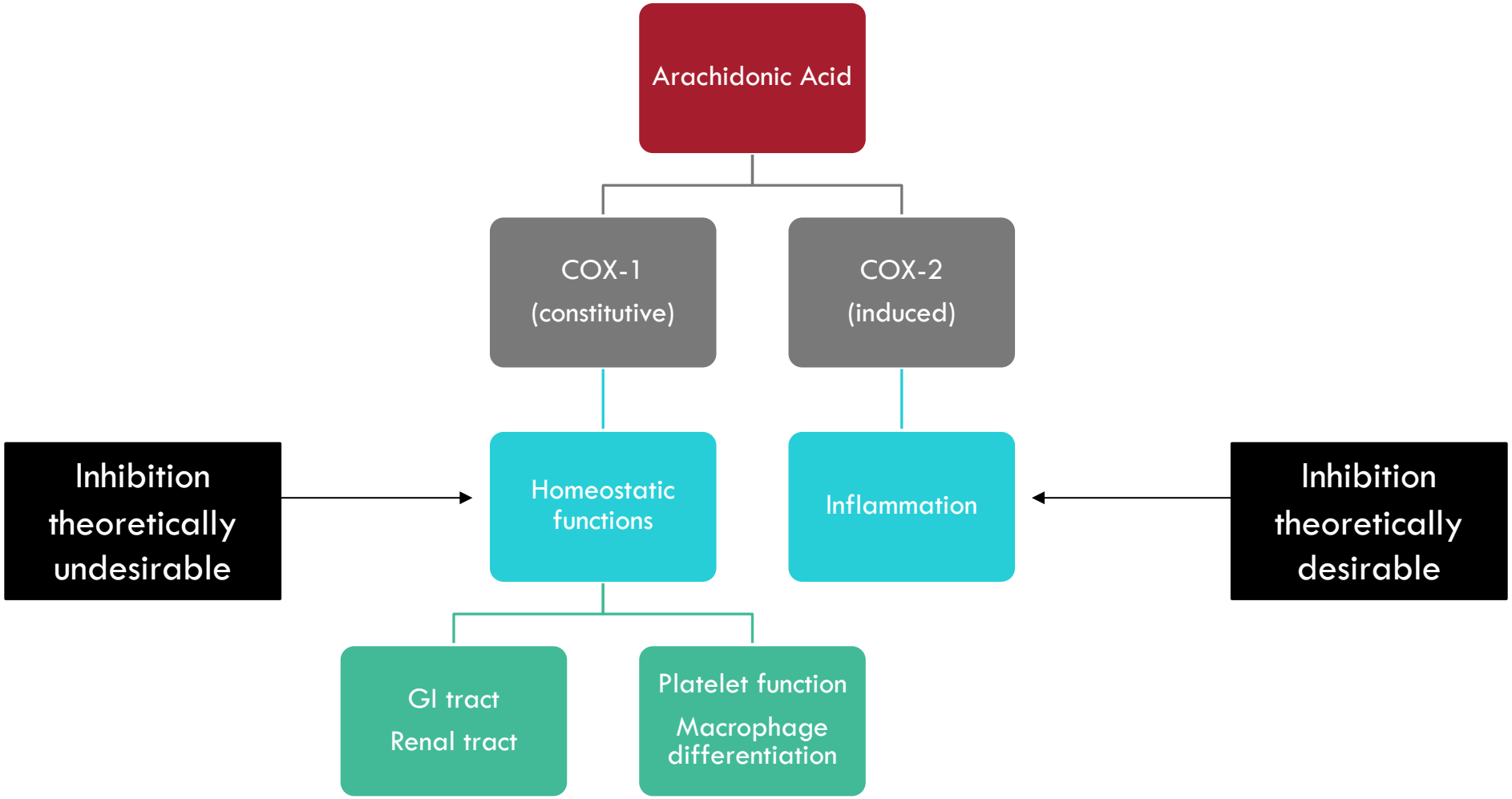
COX-2

Selectively upregulated under inflammatory conditions (inducible)

Constitutive in some areas

Responsible for production of prostaglandins such as PGE2

COX THEORY

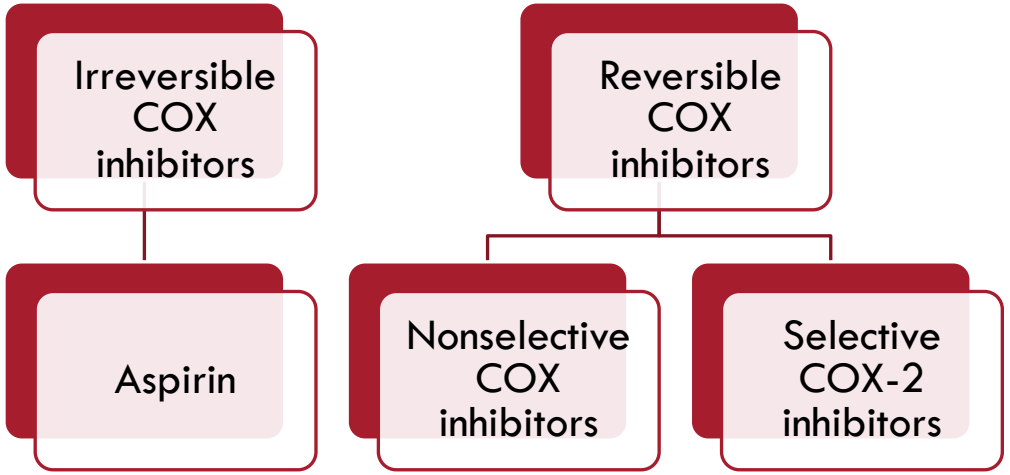

Arachidonic Acid
COX-1
(constitutive)
COX-2
(induced)
Inhibition
theoretically
undesirable
Homeostatic
functions
Inflammation
Inhibition
theoretically
desirable
GI tract
Renal tract
Platelet function
Macrophage
differentiation

ACTIVE LEARNING

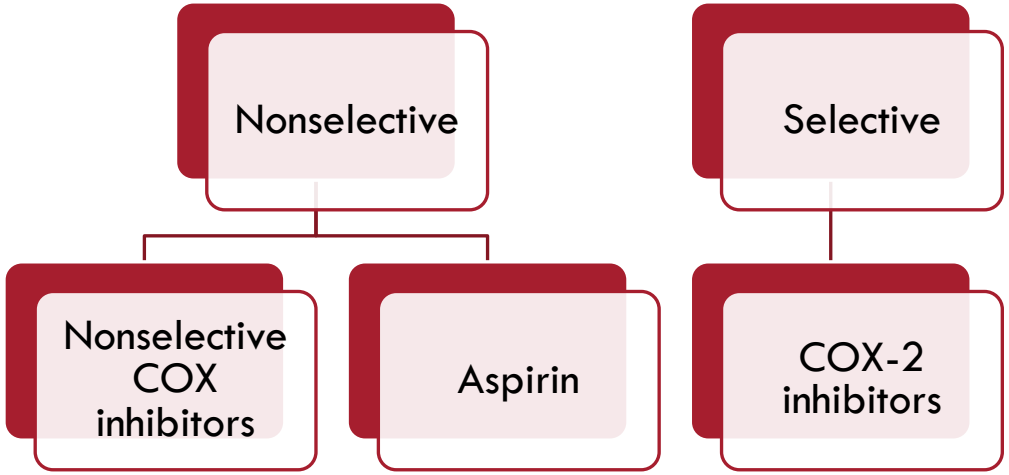
Compare and contrast COX-1 and COX-2 with someone at your table.

CLASSIFICATION OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

By Reversibility



By Selectivity



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NON-SELECTIVE COX INHIBITORS

Pharmacology

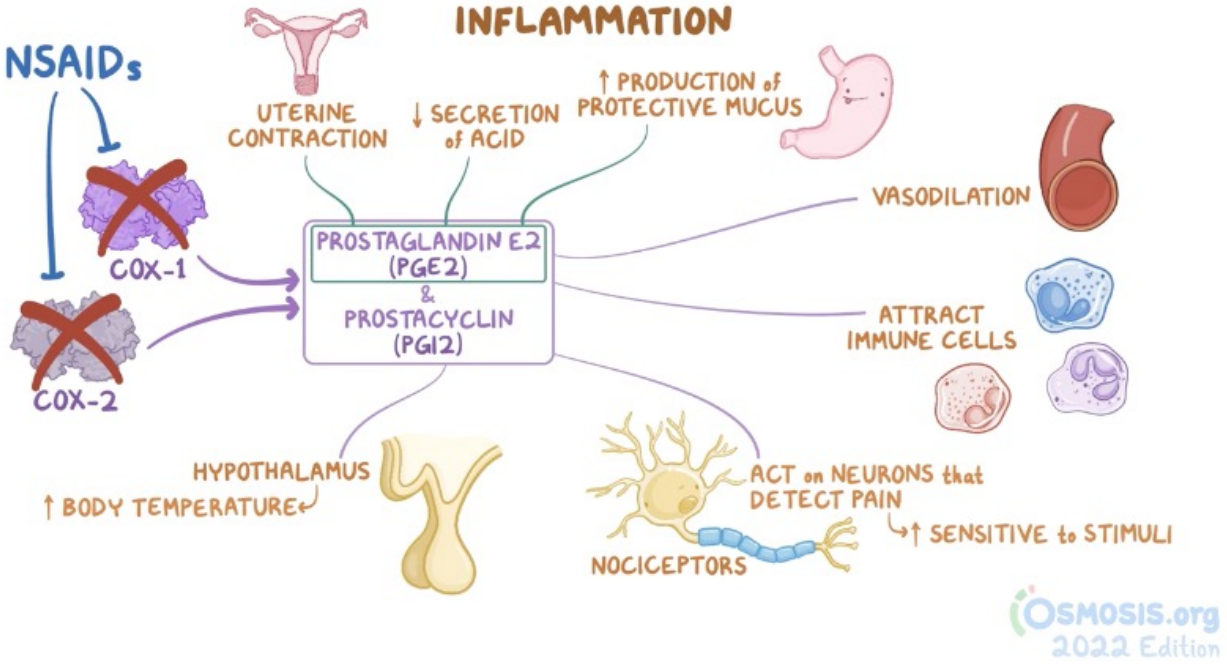
MECHANISM OF ACTION

Principal therapeutic effect via inhibition of prostaglandin production

COX inhibitors

- Inhibit prostaglandin, thromboxane, and prostacyclin synthesis

↓ sensitivity of vessels to bradykinin and histamine; ↓ lymphocyte production from T lymphocytes; reverse vasodilation and inflammation



Most NSAIDs are competitive, noncompetitive, or mixed reversible inhibitors of the COX enzymes

ACTIVE LEARNING: THE CASE OF SK

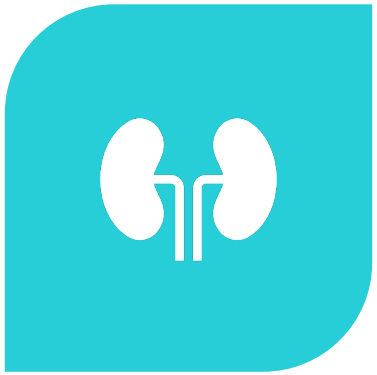
SK is considering using a nonselective NSAID to relieve her pain and inflammation. However, SK is concerned about potential side effects of any medicine she uses. Based on what we know about the mechanism of action, what side effects would you expect to be associated with nonselective NSAID use?

Take 30 seconds to write down as many as you can think of.

THREE MAIN ADVERSE EFFECTS OF NSAIDS

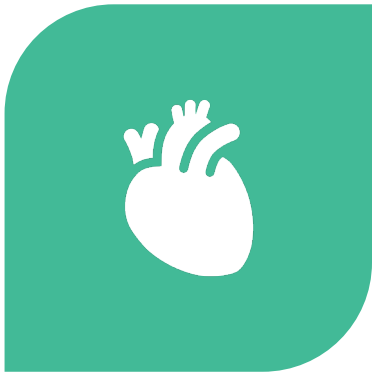
GASTROINTESTINAL

(PEPTIC ULCERS, GI BLEEDING)



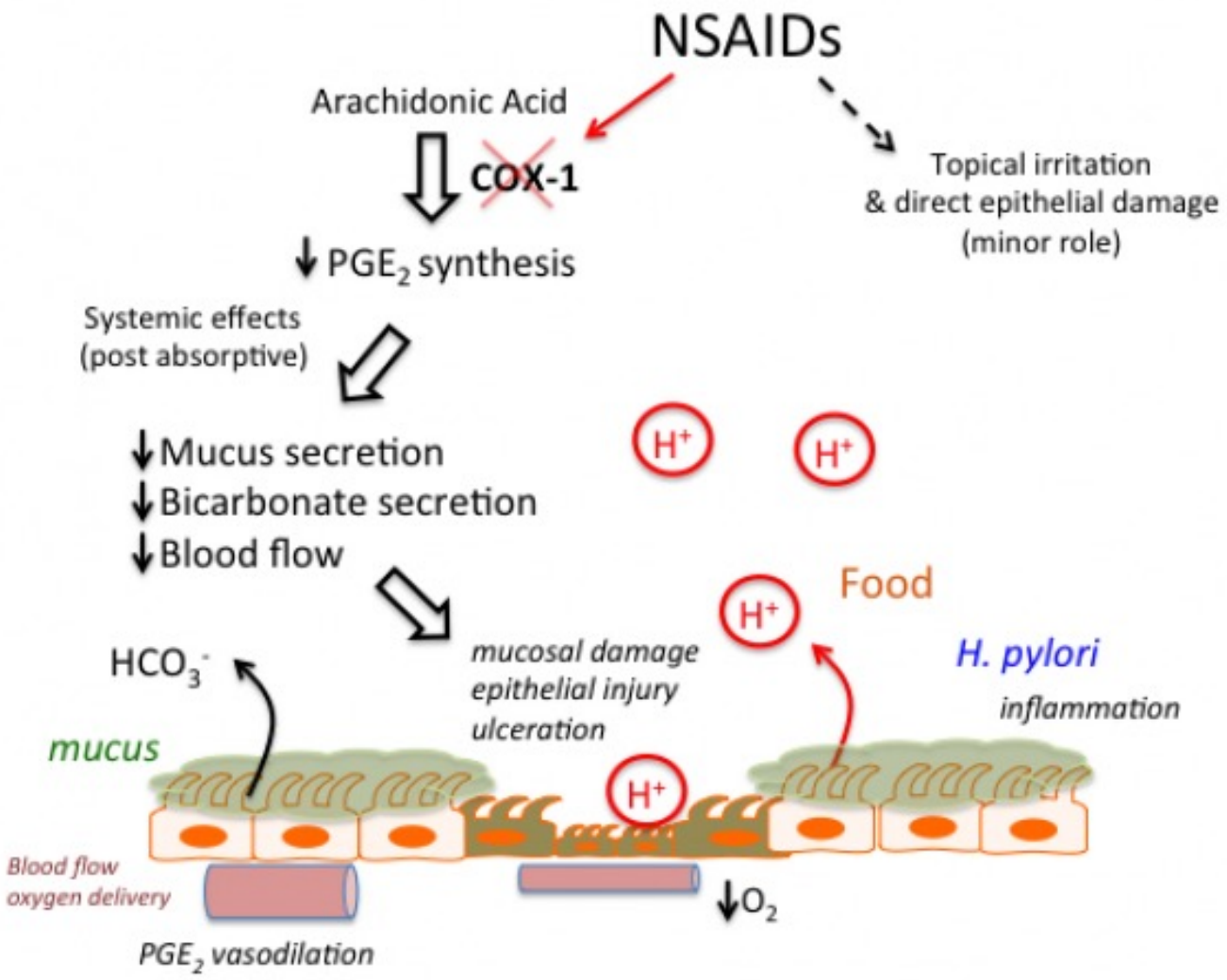
KIDNEY

NA AND H20 RETENTION, HYPERTENSION, HEMODYNAMIC ACUTE KIDNEY INJURY)

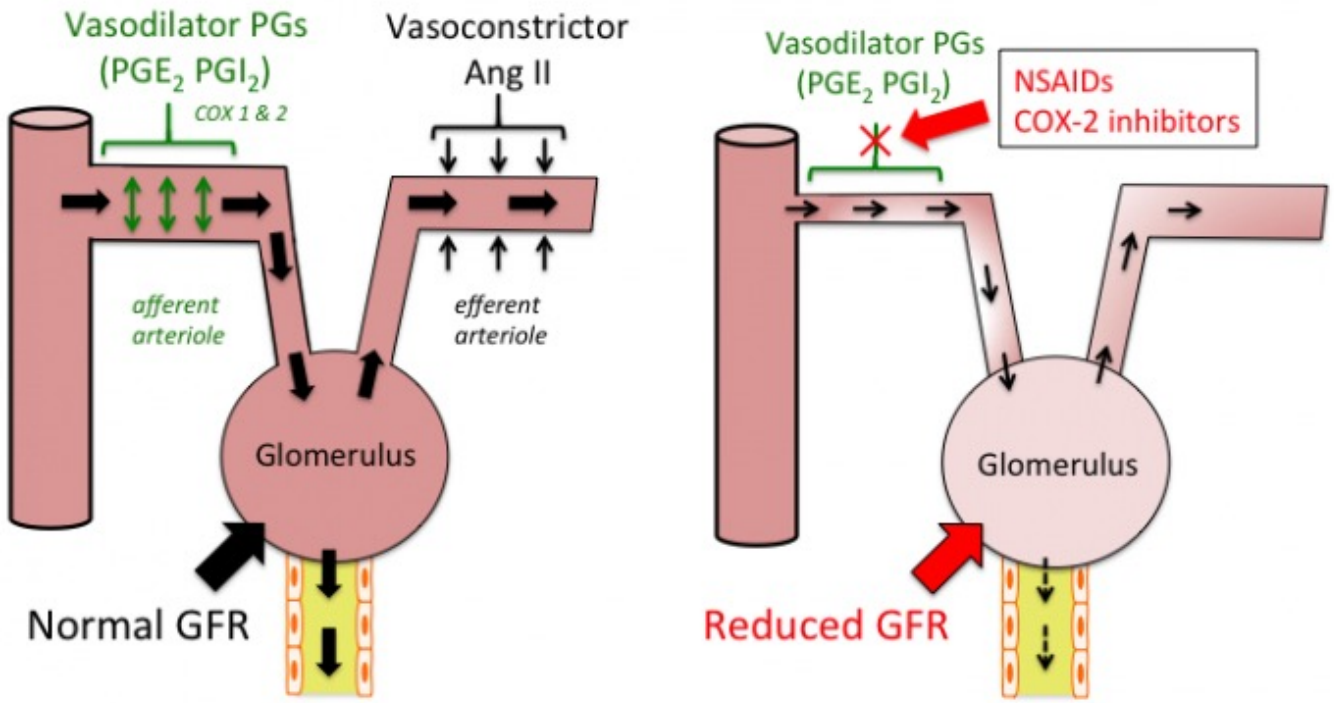


CARDIOVASCULAR

(STROKE, MYOCARDIAL INFARCTION)



GASTROINTESTINAL ADVERSE EFFECTS



KIDNEY ADVERSE EFFECTS

CARDIOVASCULAR ADVERSE EFFECTS

NSAIDs have an FDA Black Box Warning regarding the increase incidence of myocardial infarction and stroke

Proposed mechanisms include:

- NSAID-induced elevations in blood pressure
- Increase risk for kidney failure
- Reduced effectiveness of antihypertensive drugs
- Non-aspirin NSAID interference with aspirin platelet inhibition

NONSELECTIVE COX INHIBITORS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Diclofenac (Cambia) 💉 Ibuprofen (Motrin, Advil) 💉 Indomethacin (Indocin, Tivorbex) Ketorolac (Toradol) 💉 Nabumetone (Relafen) Naproxen (Aleve, Naprosyn)	Hypersensitivity **Cardiovascular thrombotic events** May increase potassium Avoid use in pregnancy (esp 3rd trimester)	Interstitial nephritis **Gastric ulcer (prostaglandins protect gastric mucosa)** **Acute kidney injury/Renal ischemia (prostaglandins vasodilate afferent arteriole)** Aplastic anemia	May increase bleeding risk of anticoagulants Increased risk of GI bleeding when used with corticosteroids May decrease efficacy of diuretics

Boxed Warning: Increased risk of cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal; increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fata

CLINICAL USES

Inflammation, pain, swelling, fever (mostly COX-2 inhibition)

Acute gout

Preterm labor

Patent ductus arteriosus (PGE2 promotes ductal patency)

PHARMACOKINETICS

A	Most organic acids; generally well absorbed
D	Highly protein bound (usually albumin); limits extracellular space distribution Accumulate in sites of inflammation (where pH is ↓)
M	Phase I, then phase II ▪ Cytochrome P450 enzymes: CYP3A4, CYP2C ▪ Phase II (direct glucuronidation)
E	Renal, varying degrees Biliary excretion and reabsorption (enterohepatic circulation)

ENTEROHEPATIC CYCLING

Liver can actively secrete ionized drugs with a molecular weight > 300 g/mol into bile

Bile flows from liver to small intestine

- Eliminated in feces
- Reabsorbed across intestinal mucosa and returned to liver via portal ciculation as part of the **enterohepatic cycle**

ACTIVE LEARNING

Nabumetone is a ketone prodrug that is metabolized to acidic active drug by CYP1A2. What would happen to the therapeutic effect of nabumetone if administered with cimetidine (a CYP1A2 inhibitor)?

OVERDOSE

No antidote

Supportive care

GI decontamination with activated charcoal can be considered if ingestion within 2 hours

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ASPIRIN

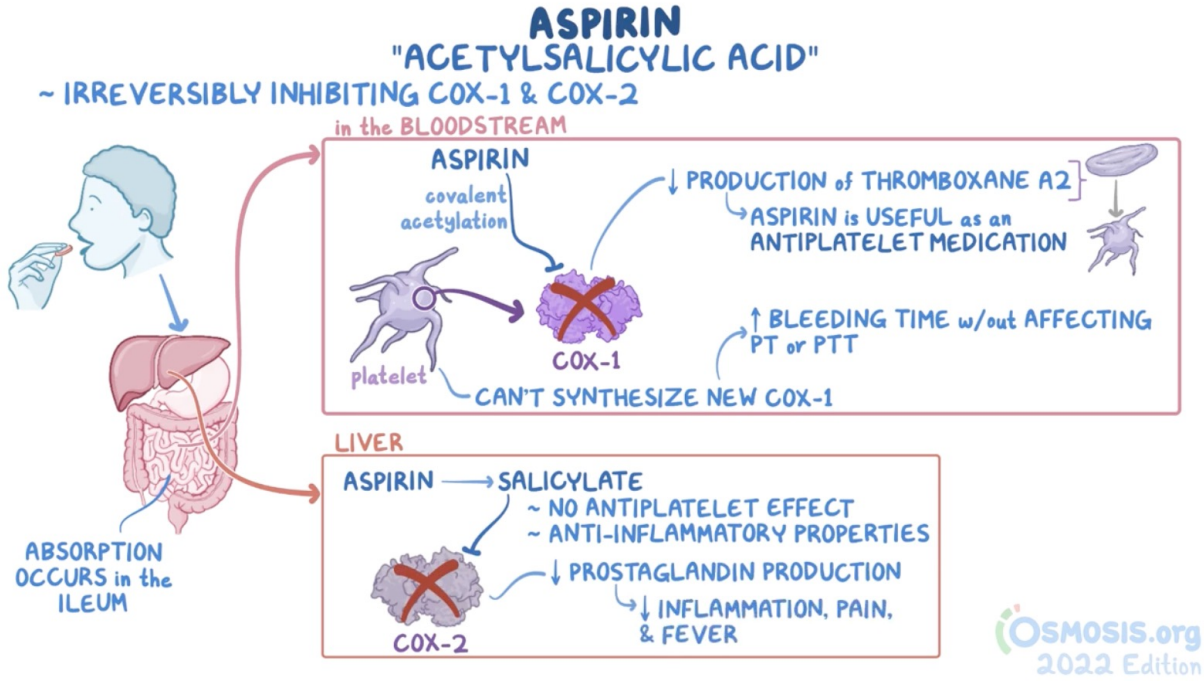
Pharmacology

MECHANISM OF ACTION

Nonselective COX inhibition

Irreversibly acetylates and blocks cyclooxygenase (COX-1 and COX-2) → ↓ synthesis of thromboxane A2 and prostaglandins → ↑ bleeding time

- Increased bleeding time due to platelet activity (no effect on prothrombin time)



ASPIRIN

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Aspirin	Hypersensitivity to NSAIDs Hemophilia **Risk of Reye's syndrome in children with viral infection** **Inhibits uric acid secretion at low doses (avoided in gout)**	**GI upset, ulcers, bleeding** **Tinnitus** **Allergic reactions** (esp nasal polyps) **Acute kidney injury** **Interstitial nephritis**	Increased risk of bleeding when used with anticoagulants Increased risk of GI bleeding when used with corticosteroids

CLINICAL USES

Prevention of stroke

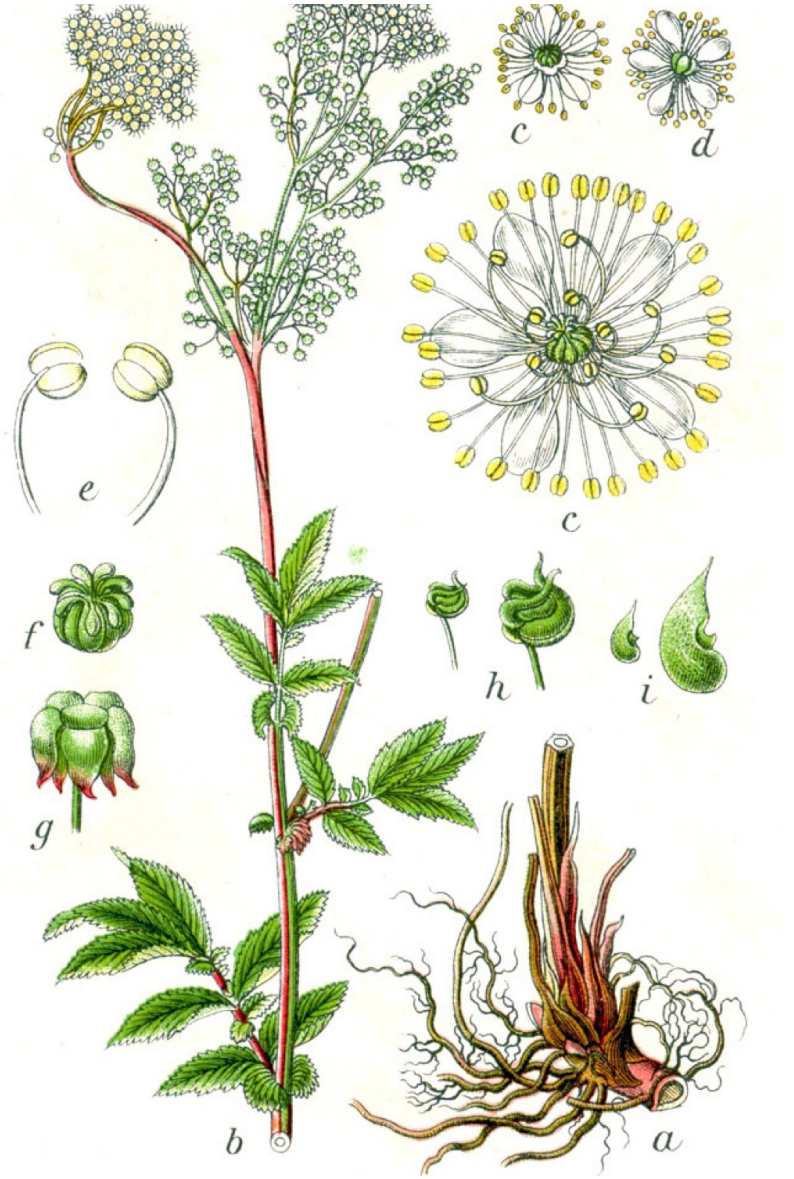
Transient ischemic attacks

Unstable angina

Coronary artery thrombosis

Thrombosis

Notes: May decrease risk of colon cancer



THE CASE OF SK

SK is deciding whether she should use aspirin for her pain and inflammation. However, she remembers reading about aspirin overdose and wants to know how much she can take and if there is an available treatment for overdose. What would you tell SK?

OPTION	MAX ADULT DAILY DOSE	OVERDOSE TREATMENT
A	4 grams	n-acetylcysteine
B	4 grams	sodium bicarbonate
C	10 grams	n-acetylcysteine
D	10 grams	sodium bicarbonate

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4 grams; sodium bicarbonate
10 grams; n-acetylcysteine
10 grams; sodium bicarbonate

PHARMACOKINETICS

A	Immediate release is rapidly absorbed from stomach; extended release depends on other factors (food, gastric pH, alcohol)
D	Concentration dependent protein binding (as concentration increases, protein binding decreases)
M	Phase I: hydrolyzed to salicylate (active) by esterases in GI mucosa, RBCs, synovial fluid, and blood Phase II: salicylate is metabolized via hepatic conjugation
E	Renal; alkalinization of urine increases the rate of excretion

OVERDOSE

Toxic doses cause respiratory alkalosis early

- Transitions to mixed metabolic acidosis-respiratory alkalosis

No antidote

Supportive care

GI decontamination with activated charcoal can be considered if ingestion within 2 hours

Sodium bicarbonate ($NaHCO_3$) to alkalinize urine to increase excretion

MANIPULATING URINARY PH

Renally cleared drugs excreted in urine by glomerular filtration and active tubular secretion

Nonionized compounds absorbed more rapidly than ionized polar molecules

- Weakly acidic drugs susceptible to "ion trapping" in the urine
  - Aspirin weak acid with a pKa = 3.0
  - As pH of urine increases (alkalinizes), more salicylate is in the ionized form at equilibrium
    - More salicylic acid diffuses into tubular lumen of the kidney

Alkalinize urine with sodium bicarbonate (NaHCO3)

- Contraindicated in renal failure or if fluid administration may worsen symptoms (pulmonary edema, heart failure)

WEAK ACIDS (SUCH AS ASPIRIN)

$$HA \leftrightarrows H^+ + A^-$$

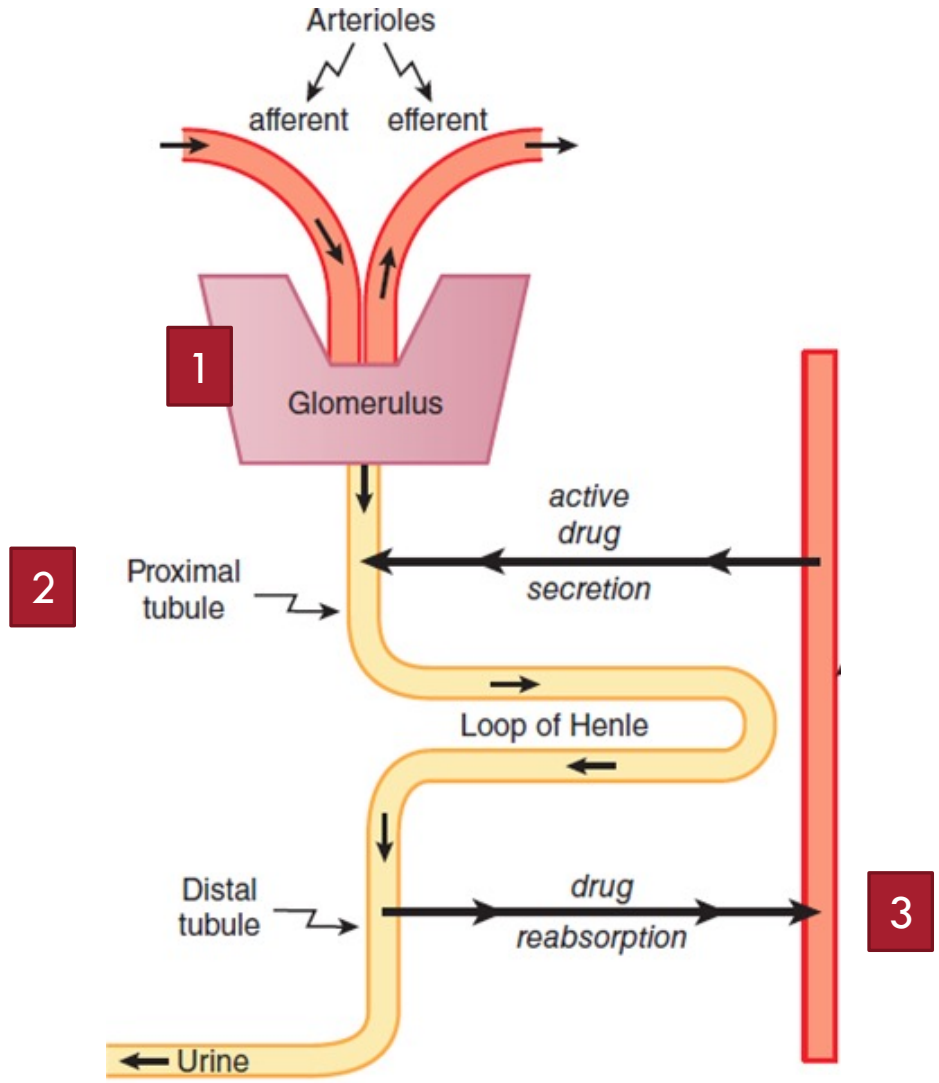
pK is the equilibrium constant

- pH = pK, there are equal amounts of weak acid in the ionized and nonionized forms
- pH < pK (add more H^+), drive the equilibrium to the left and there is more protonated (nonionized) form
- pH > pK (take away H^+), drive the equilibrium to the right and there is more unprotonated (ionized) form

RENAL EXCRETION

3. Distal tubular reabsorption

- Uncharged drugs may diffuse out of the kidney and escape elimination
- Manipulating the pH of the urine may alter this process by changing the ionization of the weak acids and bases
- For a drug to be excreted, it needs to be charged so that it is trapped in the urine and can't cross the membrane to sneak back into the body
- Urine flow rate impacts reabsorption; ↑ flow rate ↓ time available for drug to move across cell membrane and back into blood



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COX-2 INHIBITORS

Pharmacology

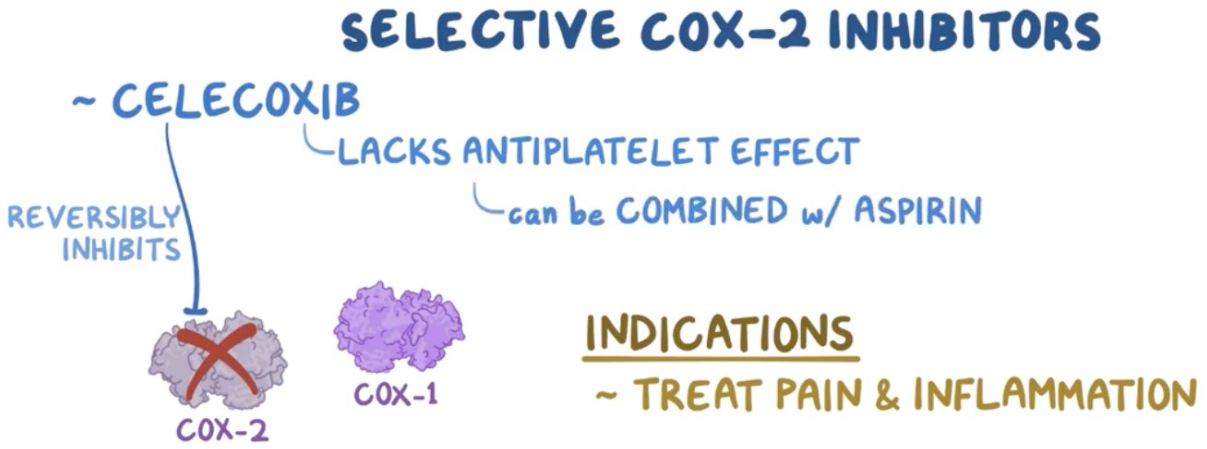
MECHANISM OF ACTION

Selectively inhibit prostaglandin by primary COX-2 inhibition

- COX-2 primarily found in inflammatory cells and vascular endothelium – mediates inflammation and pain

- Spares COX-1
  - Helps maintain gastric mucosa
  - Spares platelet function (thromboxane A2 production is dependent on COX-1)

Reversible inhibition



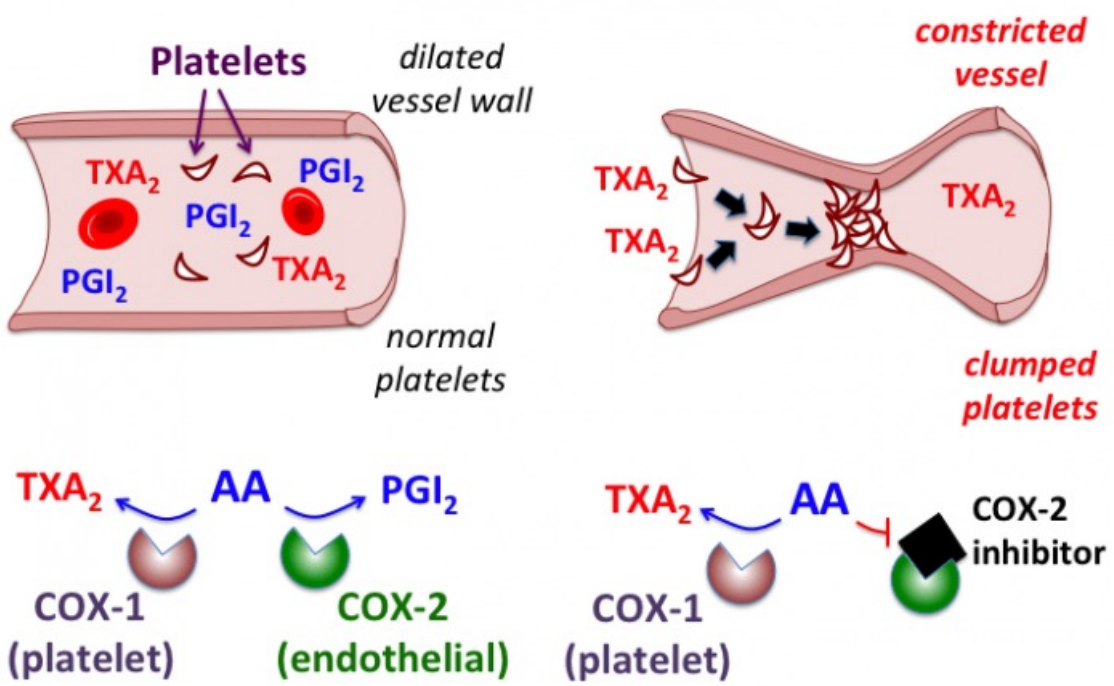
COX-2 INHIBITOR

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Celecoxib (Celebrex)	Hypersensitivity to NSAIDs, sulfa (cross reaction) Cardiovascular thrombotic events Increased risk of serious GI events	Increased risk of thrombosis	Increased risk of bleeding when used with anticoagulants Increased risk of GI bleeding when used with corticosteroids

SELECTIVE COX-2 INHIBITION & INCREASED CARDIOVASCULAR RISK

Greater COX-2 vs COX-1 inhibition can tip balance between effects of prostacyclin and thromboxane

- ↑ likelihood for platelet aggregation and vasoconstriction



CLINICAL USES

Acute pain

Ankylosing spondylitis

Osteoarthritis

Primary dysmenorrhea

Rheumatoid arthritis

PHARMACOKINETICS

A	Prolonged due to low solubility
D	Highly protein bound (albumin)
M	Phase I: CYP2C9; forms inactive metabolites
E	Feces and urine

REFERENCE LIST

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ANY QUESTIONS?