MINI MED SCHOOL

Talk 8: How to avoid a drug interaction

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a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA
Faculty of Medicine

University of Victoria

let's talk science

TERRITORIAL ACKNOWLEDGEMENT

I would like to begin by acknowledging that I am joining you from the unceded territory of the Coast Salish Peoples, including the territories of the xwməθkwəy̓əm (Musqueam), Skwxwú7mesh (Squamish), Stó:lō and Səlílwətaʔ/Selilwitulh (Tsleil- Waututh) Nations.

I would also like to acknowledge the Lekwungen peoples on whose traditional territory the University of Victoria stands and the Songhees, Esquimalt and Wsanec peoples whose historical relationships with the land continue to this day.

DISCLOSURE

I am a medical student. These talks do not constitute or substitute for medical advice.

Please consult with your healthcare provider or pharmacist if you have questions about your specific health situation.

TOPICS

- Pharmacodynamic interactions
  - Additive or antagonistic
- Pharmacokinetic interactions
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
- Drug-Food and Drug-Disease interactions

True or False: When my doctor asks which medications I'm on, they only really want to know my prescription medications.

A. True
B. False

True or False: When my doctor asks which medications I'm on, they only really want to know my prescription medications.

A. True

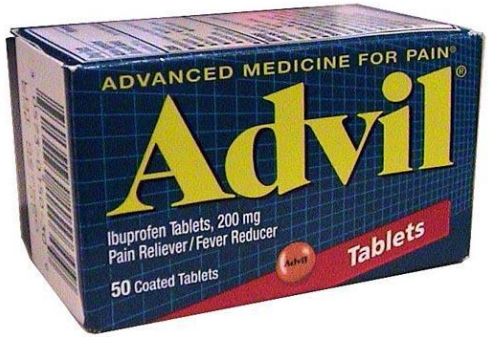
B. False

ADDITIVE INTERACTIONS

- Taking two or more medications that have similar effects get heightened effect potentially toxic at higher doses if done unintentionally or produce unwanted side effects

- Simple examples:
  - Acetaminophen/Tylenol + other cold & flu medications (i.e.. Nyquil)

NSAIDS + LOTS OF THINGS

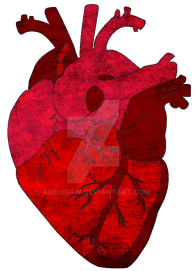


- Used for pain relief
- Additive
  - If combined with anti-depressants (citalopram, fluoxetine, sertraline etc.) or glucocorticoids increased risk of bleeding

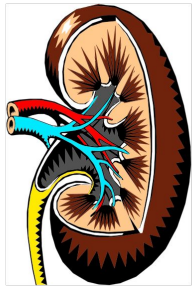
- Antagonistic
  - If combined with aspirin increased cardiac risk in coronary heart disease patients

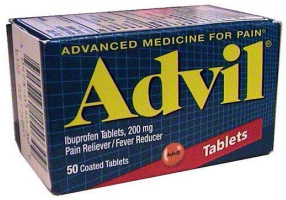
ACE-INHIBITORS + LOTS OF THINGS

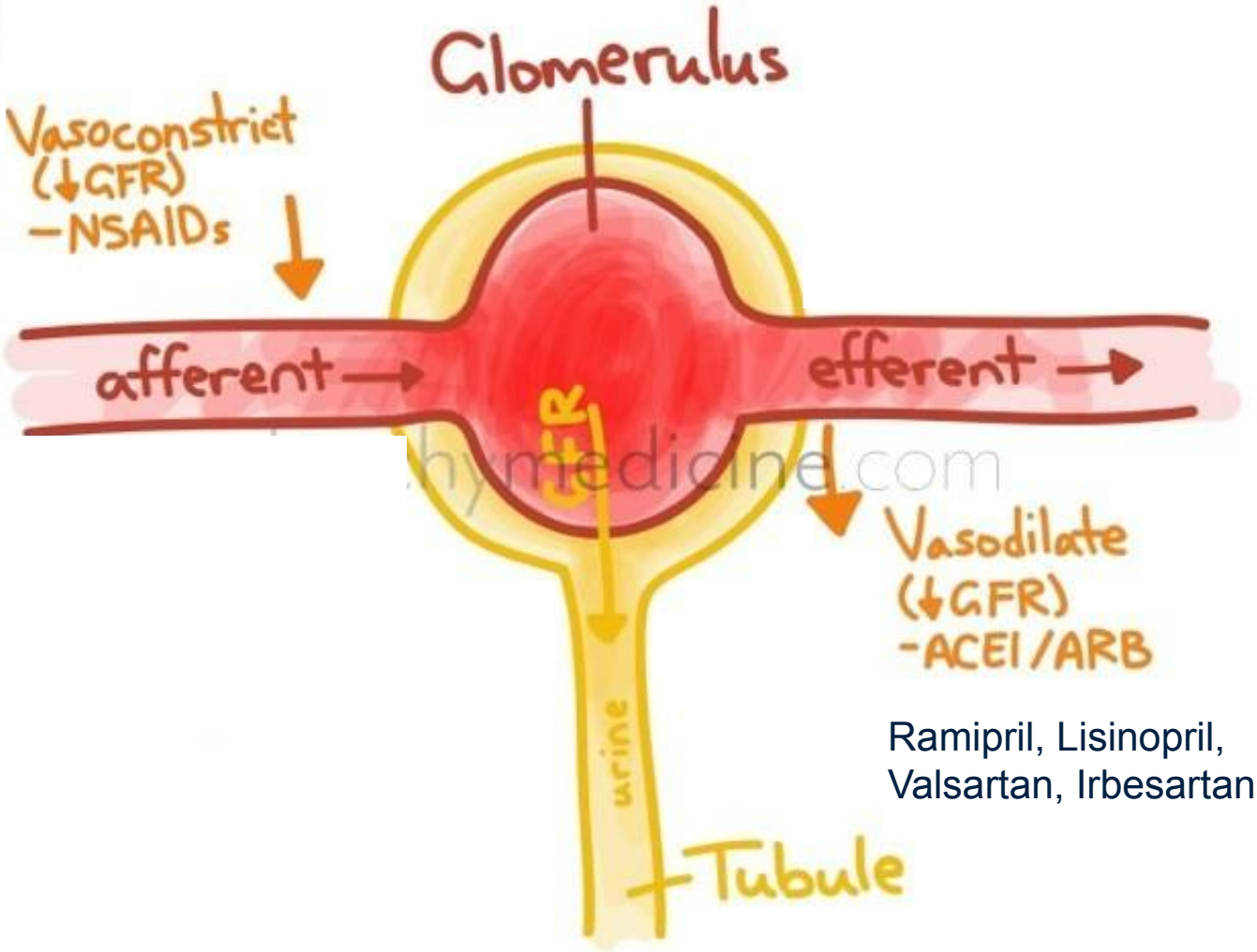
- Additive
  - If combined with potassium-sparing diuretics (spironolactone or amiloride) elevated potassium



- Antagonistic
  - If combined with NSAIDs reduced effects and risks of acute kidney injury.







Ramipril, Lisinopril,
Valsartan, Irbesartan etc.

SEROTONIN SYNDROME

- When two medications are added that both elevate serotonin can achieve super high levels of serotonin, leading to serotonin syndrome
- **Examples:** anti-depressants (SSRI or SNRIs), bupropion, opioids, anti-migraine medication, anti-nausea medications, herbal supplements etc.

- **Mild symptoms:** agitation, insomnia, confusion, shivering etc.
- **Severe symptoms:** fever, tremor, seizures, irregular heartbeat

TABLE 1

Examples of typical additive and antagonistic pharmacodynamic interactions

Substance I	Substance II	Possible effect
Additive interactions		
NSAIDs	SSRI, phenprocoumon	Increased risk of bleeding
NSAIDs	Glucocorticoids	Increased risk of gastric bleeding
ACE inhibitors	Spironolactone, amiloride	Hyperkalemia
SSRIs	Triptans	Serotonin syndrome
Tricyclic antidepressants	Low-potency neuroleptics	Increased anticholinergic effects
Quinolones	Macrolides, citalopram	QT-interval prolongation, torsade de pointes
Antagonistic interactions		
Acetylsalicylic acid	Ibuprofen	Reduced effects
ACE inhibitors	NSAIDs	Reduced effects
Levodopa	Classical neuroleptics	Reduced effects
Phenprocoumon	Vitamin K	Reduced effects

SSRI, selective serotonin reuptake inhibitor; NSAID, nonsteroidal anti-inflammatory drug

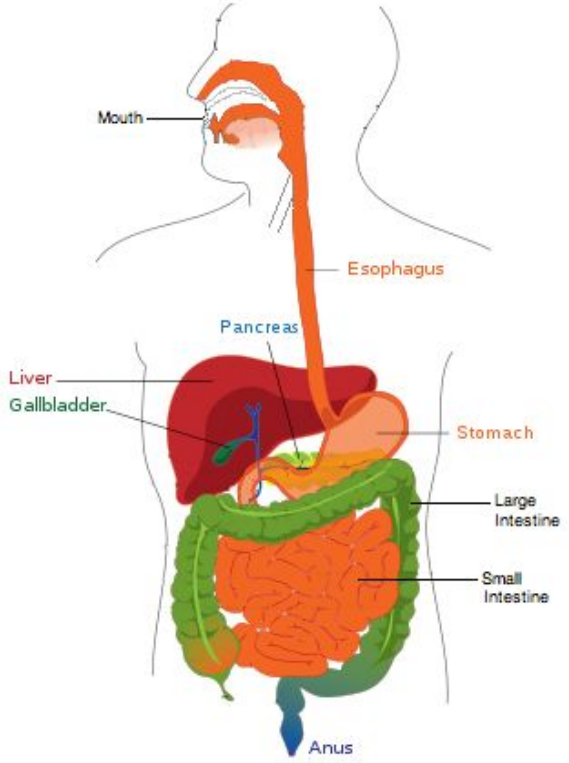
Cascorbi I. (2012). Drug interactions--principles, examples and clinical consequences. *Deutsches Arzteblatt international*, *109*(33-34), 546–556. https://doi.org/10.3238/arztebl.2012.0546

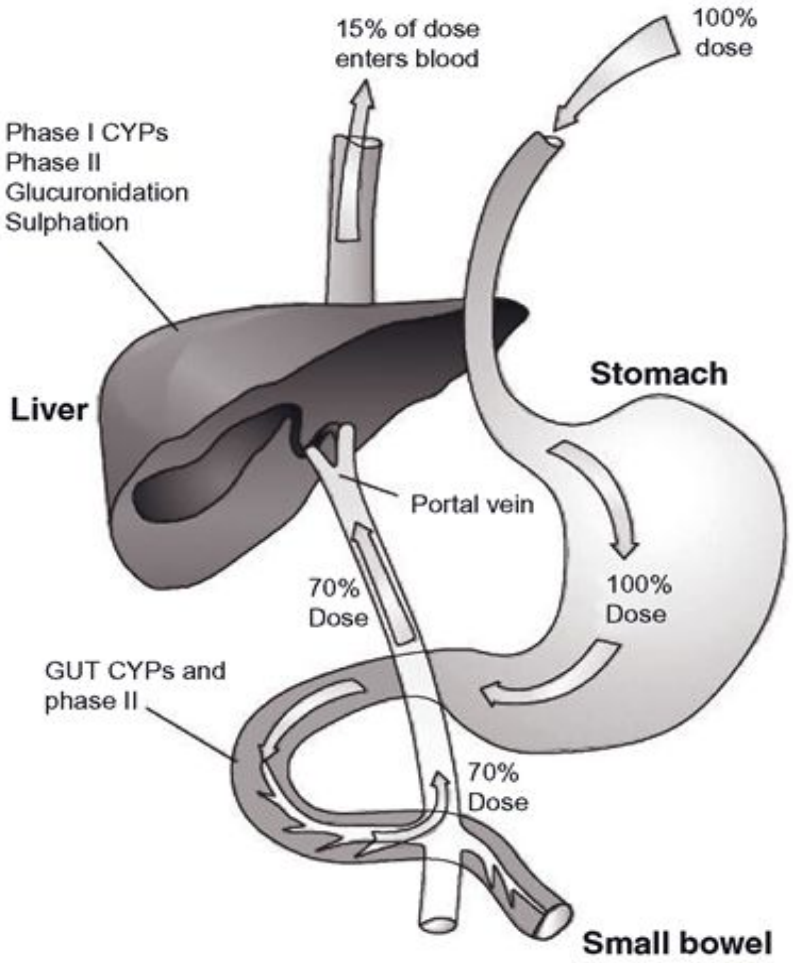
DRUG METABOLISM: ADME

- ABSORPTION
- DISTRIBUTION
- METABOLISM
- EXCRETION

PATH OF AN ORAL MEDICATION

- Mouth
- Stomach
  - Potential modifiers: acid
- Small Intestine
  - Potential modifiers: transporters
- Liver
  - Potential modifiers: enzymes, other medications, disease
  - “First pass metabolism” □ drug concentrations reduced at the liver



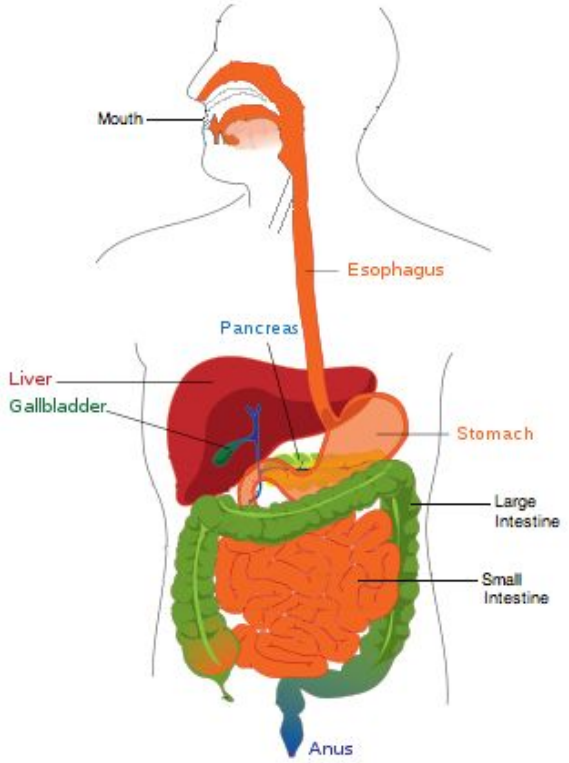


https://what-when-how.com/human-drug-metabolism/first-pass-and-plasma-drug-levels-introduction-human-drug-metabolism/

PATH OF AN ORAL MEDICATION

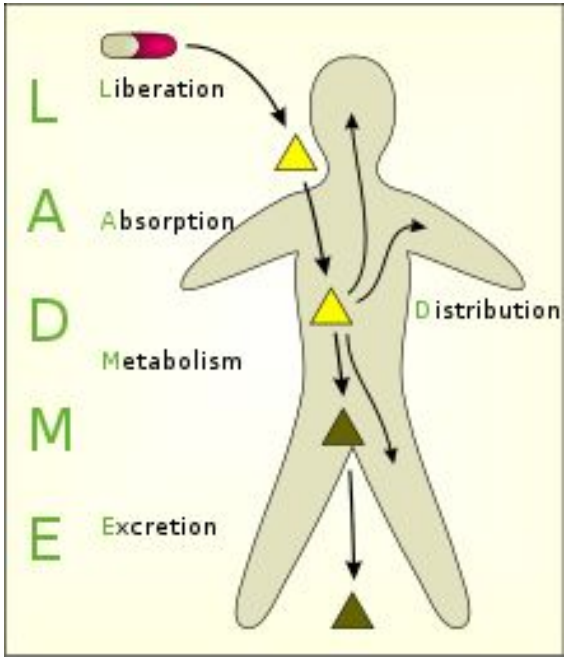
- Blood
  - Potential modifiers: plasma proteins
- Target organs

- Once inactive:
- Removed via the kidneys urine
- OR via the liver bile feces



DRUG METABOLISM: ADME

- <u>Absorption: How the drug gets into the body</u>
  - Mainly through digestive tract (except intravenous (IV)
  - Important for oral medication
  - Changes in stomach pH can alter absorption
  - Certain medications can increase or reduce the bioavailability of other medications through modifying p-glycoproteins



True or False: TUMS and other anti-acids are harmless

A. True

B. False

True or False: TUMS and other anti-acids are harmless

A. True

B. False

TUMS (CALCIUM CARBONATE)

- TUMS neutralizes stomach acid □ alters the way medications are processed in the stomach
    - May decrease the bioavailability of medication (decreased effect)
    - May bind and form complexes with the medication □ medication can’t go on and exert its effect

Recommendation: Take only as needed, and at least 2 hours before or after taking other medications

P-glycoproteins are transporters in the gut that control how much drug is absorbed.

- **Inducers** of P-glycoprotein decreases the absorption/effect of a drug

- **Inhibitors** of P-glycoprotein increases the absorption/effect of a drug

- **Substrates** are medications that are especially reliant on this pump

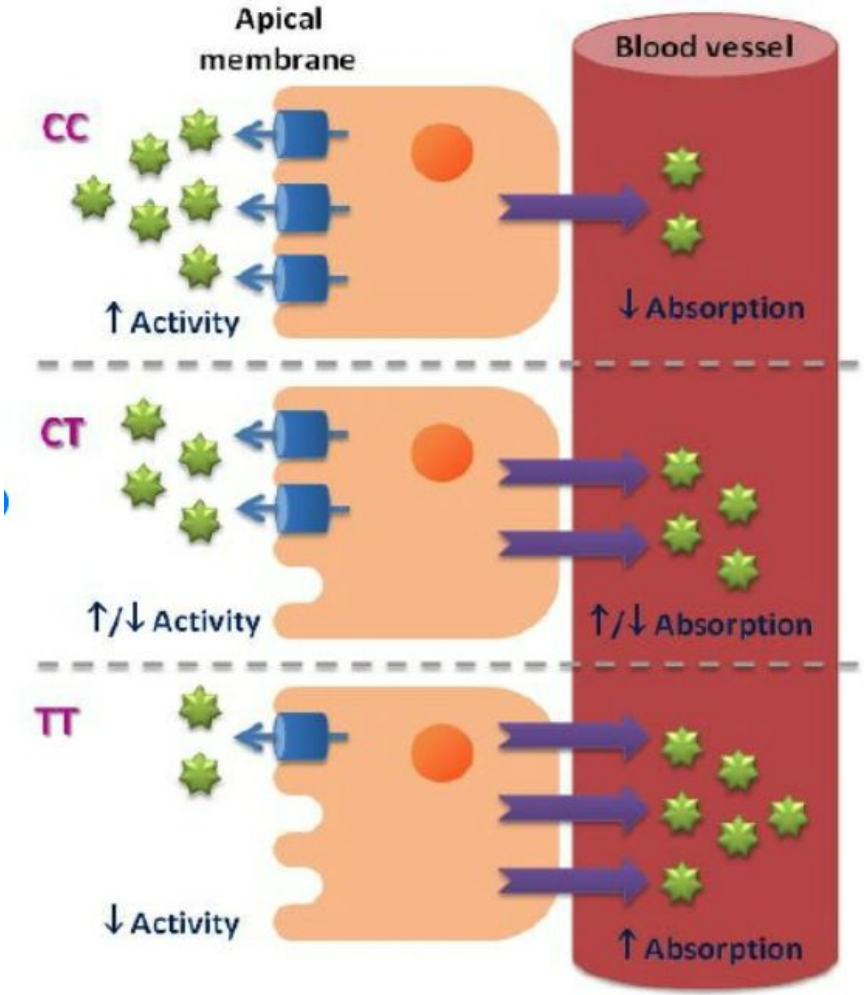
TABLE 2

Examples of interactions at the intestinal absorption level: selection of relevant substrates, inducers, and inhibitors of P-glycoprotein (ABCB1)

Group	Substance
Substrates	
Opioids	Loperamide, morphine
Antihypertensives	Aliskiren, carvedilol
Anticoagulants	Dabigatran
Cardiac glycosides	Digoxin
Immunosuppressants	Ciclosporin, tacrolimus, sirolimus
Protease inhibitors	Indinavir, saquinavir
Statins	Atorvastatin, lovastatin, simvastatin
Antineoplastic agents	Paclitaxel, anthracyclines, vinca alkaloids, etoposide, imatinib
Inducers	
Anticonvulsants	Carbamazepine (oxcarbazepine less so), phenytoin, phenobarbital, primidone
Tuberculostatics	Rifampicin
Antiretroviral	Efavirenz
St. John's wort extract	Hyperforin
Inhibitors	
Antimycotics	Itraconazole, ketoconazole
Calcium channel blockers	Diltiazem; felodipine; nicardipine; nifedipine; verapamil especially
Macrolide antibiotics	Erythromycin, clarithromycin, not azithromycin
HIV protease inhibitors	Indinavir; nelfinavir; ritonavir especially; saquinavir
Immunosuppressants	Ciclosporin
Antiarrhythmic drugs	Amiodarone, quinidine, propafenone

Inducers

Inhibitors



Practical Pharmacogenetics and Single Nucleotide Polymorphisms (SNPs) in Renal Transplantation - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Influence-of-the-functional-activity-of-glycoprotein-P-transporter-in-apical-membrane_fig2_258405288 [accessed 12 Feb, 2022]

ST. JOHN'S WORT

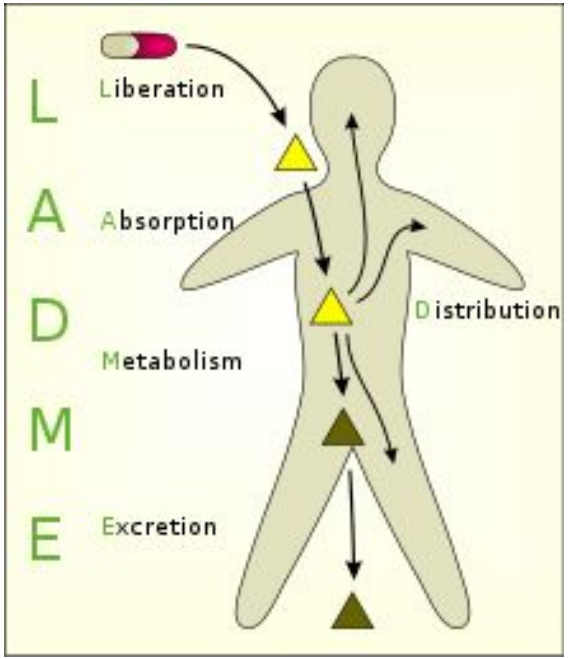
- A five-petal flower that was originally used to prevent demonic possession and "evil spirits"

- Now claimed to help as an anti-depressant and possess potential anti-inflammatory or wound healing properties
    - **Limited evidence in humans**

- **SEVERAL medication interactions**

DRUG METABOLISM: ADME

- Distribution: how the drug leaves the bloodstream and gets to the tissues
  - Not a big issue for drug interactions
  - Protein binding will deactivate most drugs
  - May be an issue with situations of fluid overload end-stage liver disease, heart failure, end-stage kidney disease etc.



DRUG METABOLISM: ADME

- Metabolism: irreversible transformation of drug “first-pass metabolism”
- Mainly in the liver
  - Phase 1: Cytochrome P450 enzymes
  - Phase 2: Non-P450 enzymes
- Doesn’t apply to intravenous medications

- BIG area for interactions

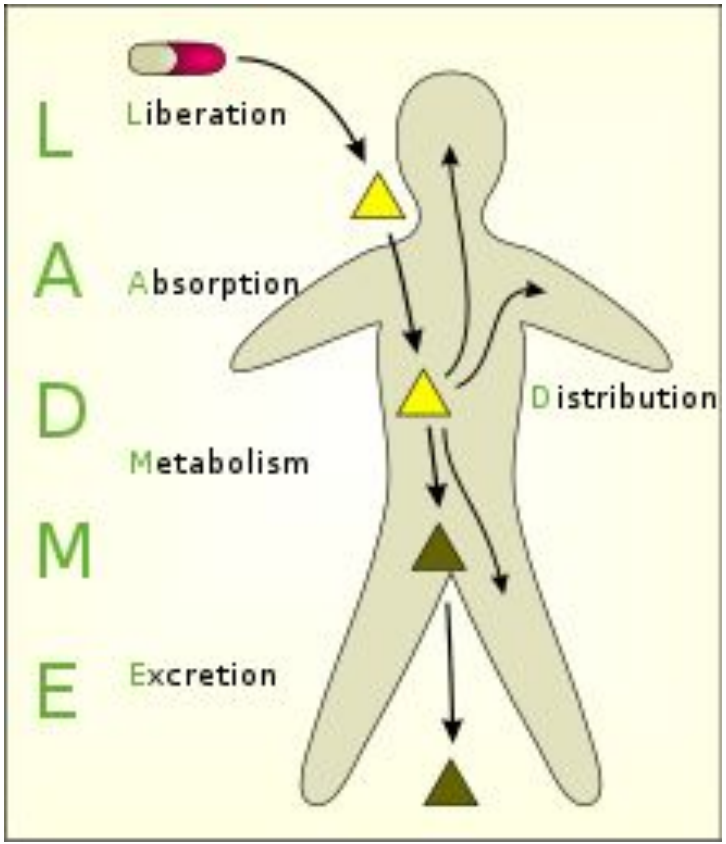
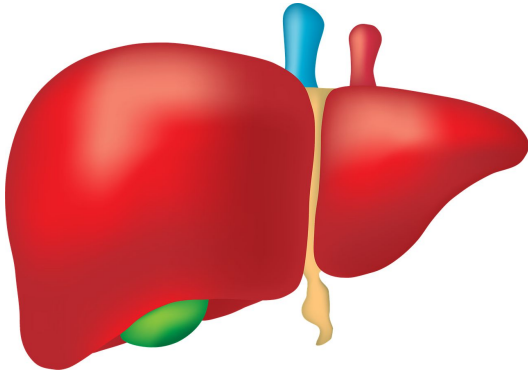


TABLE 4

Interactions with the most important cytochrome P450 enzymes: inhibitors and inducers (modified from [25])

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5
Inhibitors				
Fluoroquinolones Ciprofloxacin ++ Ofloxacin Levofloxacin **Miscellaneous** Amiodarone Cimetidine + Fluvoxamine ++ Ticlopidine	Amiodarone + Fluconazole ++ Isoniazide	**SSRIs** Fluoxetine Fluvoxamine **PPIs** Lansoprazole + Omeprazole + **Miscellaneous** Ketoconazole Ticlopidine	**SSRIs** Duloxetin + Fluoxetine ++ Paroxetine ++ **Miscellaneous** Amiodarone Buproprion Cimetidine Quinidine ++ Chlorphenamine Clomipramine Ritonavir	**HIV protease inhibitors** Indinavir ++ Nelfinavir ++ Ritonavir ++ **Macrolides** Clarithromycin ++ Erythromycin + **Azole antimycotics** Fluconazole + Itraconazole + Ketoconazole ++ Voriconazole **Miscellaneous** Aprepitant +, Amiodarone Cimetidine + Diltiazem Naringin + (in citrus fruits) Verapamil +
Inducers				
Tobacco smoke Omeprazole	Rifampicin			Carbamazepine (oxcarbazepine less so) Efavirenz Hyperforin (in St. John's wort) Phenobarbital Phenytoin Rifampicin

LIVER DISEASE

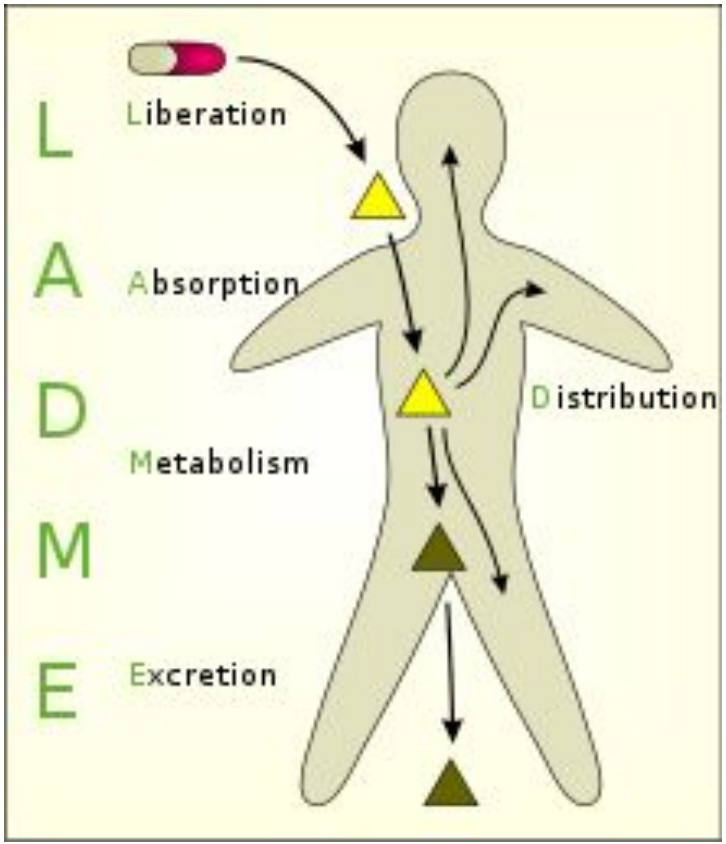


- Advanced liver disease (cirrhosis) can decrease certain drug metabolizing enzymes and can affect excretion via bile and the kidneys
- Reduced production of plasma proteins (albumin)
  □ more free (active) drug
    - This may lead to drug accumulation □ toxic effects

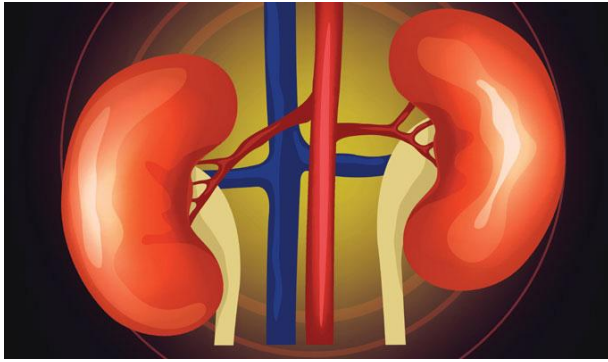
- It’s likely that a decrease in dose is needed for certain medications.

DRUG METABOLISM: ADME

- Excretion: how the drug leaves the body
  - Mostly happens in the kidneys
    - Implications for kidney disease
  - Can also be excreted through bile
    - feces



KIDNEY DISEASE



- Similar to liver disease, any issues in excreting a drug may increase the drug levels in the body, especially those dependent on kidney metabolism

- Severe kidney disease causes changes in nonrenal clearance (i.e. Liver), protein binding and volume of distribution

BREAK TIME!

DRUG-FOOD INTERACTIONS

GRAPEFRUIT (JUICE)

- Blocks the action of CYP3A4 enzyme in the liver potential for drug accumulation and more side effects/toxicity

- Particularly for:
  - Statins (i.e. Simvastatin, atorvastatin)
  - Calcium channel blockers (i.e. Nifedipine)
  - Immunosuppressants (i.e. Cyclosporine)

ALCOHOL

- Alcohol IS a drug depresses the central nervous system

- Can magnify side effects i.e. Drowsiness

- Can affect liver enzymes
  - Lowers the toxic threshold of Tylenol

WARFARIN AND VITAMIN K

- Lots of drug-drug interactions

- Acts by inhibiting vitamin K reductase
  - Vitamin K found in some foods cancels out warfarin

- Be wary of multivitamins may contain vitamin K

LICORICE

- Eating 2 ounces a day for over 2 weeks can lead to an arrhythmia!
- Contains glycyrrhizin lowers potassium

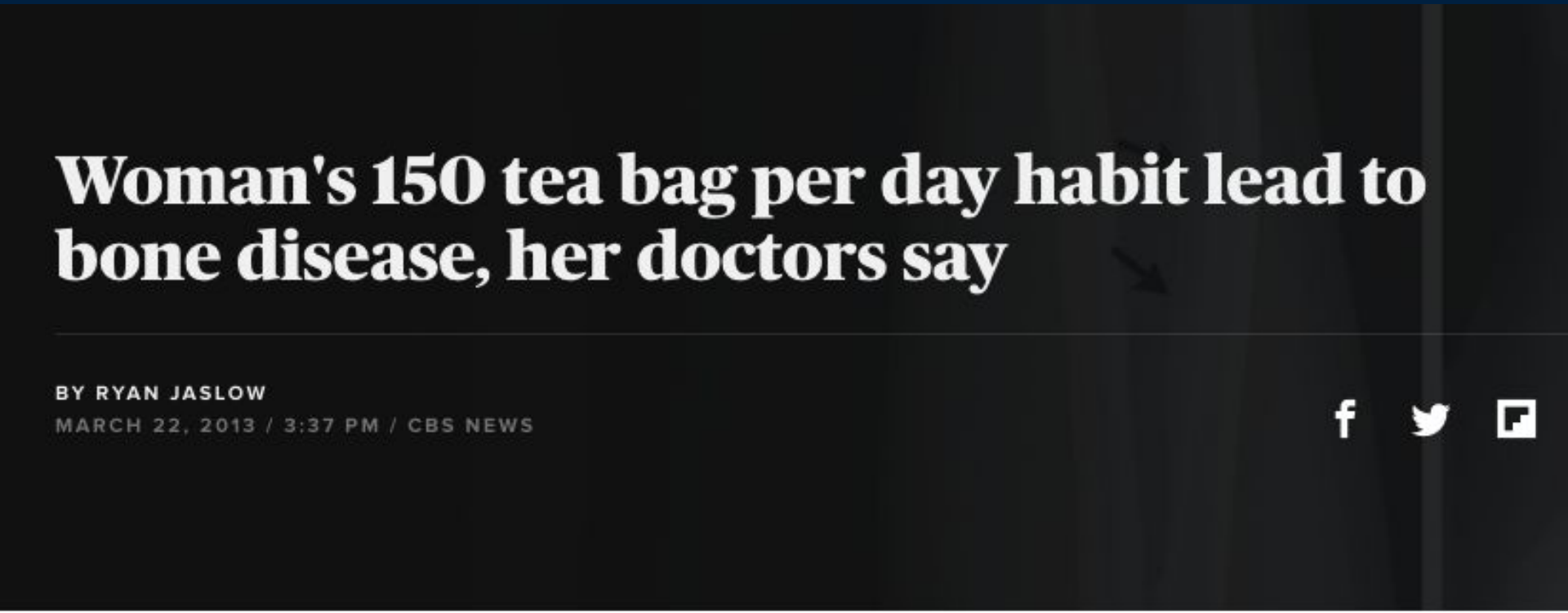
- Low potassium can be life-threatening abnormal heart rhythms, hypertension, swelling, lethargy and congestive heart failure

- Try to avoid if taking medications that also lower potassium (i.e. diuretics)

POTASSIUM

- Elevated potassium (hyperkalemia) can be a side effect of many common medications
  - ACE-Inhibitors (ramipril, lisinopril etc.)
  - Angiotensin 2 receptor blockers (valsartan etc.)
  - NSAIDs (ibuprofen, naproxen)
  - Immunosuppressants (cyclosporine, tacrolimus)

- Important to have electrolytes checked, especially when first starting a medication. If high potassium is an issue change medication or reduce foods


Woman's 150 tea bag per day habit lead to bone disease, her doctors say
BY RYAN JASLOW
MARCH 22, 2013 / 3:37 PM / CBS NEWS

GREEN TEA

- Interacts in a few ways:
- Contains caffeine certain medications decrease metabolism of caffeine You might feel a bit jittery
- Green tea and green tea extract Can decrease absorption and bioavailability of certain drugs
    - Atorvastatin (Lipitor), lisinopril, cancer medications, blood thinners etc..

DRUG-DISEASE INTERACTIONS

BETA-BLOCKERS + ASTHMA

- Beta blockers (metoprolol, labetalol etc.) work by blocking beta receptors throughout the body decreased heart rate, contractility, lower blood pressure
- Asthma medications help widen the airways and reduce inflammation by binding beta receptors

- If you take beta-blockers and have asthma your asthma will get worse
    - Usually contraindicated

NASAL DECONGESTANTS

- Significant drug-disease interaction for those with cardiovascular disease
- Work by vasoconstricting the vessels in the nasal mucosa reduced congestion

- BUT some medication can go systemically
  - Narrowing of other vessels (i.e.. Coronary vessels) NOT GOOD

True or False: There's a website that my doctor can check which medications I'm on, so it's okay if I forget to mention some.

A. True
B. False
C. It depends

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A. True
B. False
C. It depends

PHARMANET

- A website where physicians and pharmacists in BC can look up which medications you're on.

- Doesn't include:
  - Over-the-counter medications (unless prescribed)
  - Supplements, vitamins, herbal remedies
  - Medications you received as a sample from the doctor
  - Prescriptions you haven't filled
  - Any prescriptions filled outside BC
  - Medications dispensed by certain agencies i.e. BC Cancer

TIPS TO AVOID A DRUG INTERACTION

1) Make a list of your medications and take it with you to appointments.
2) Stick to one pharmacy if you can.
3) Inform your primary care provider of any new medication, supplement, vitamin, herbal remedy that you are taking.
4) Over-the-counter medications ARE medications (i.e. Ibuprofen, Tylenol)
5) Make sure your medications are properly labelled. Daily pill containers can help, or you can ask for blister packing at the pharmacy.
6) Read the inserts that are given with new medications.
7) If you're having trouble taking oral medications, ask your doctor/pharmacist for alternatives.
8) If in doubt, ASK!

HELPFUL RESOURCES

- Your healthcare provider or pharmacist! Ask for a full medication review.

- Health Link BC or 811
- Health Gateway

- Drug interaction checkers:
- https://www.drugs.com/drug_interactions.html

FUTURE TALKS

- Sunday Feb 20: Supplements

We hope to see you there!

THE UNIVERSITY OF BRITISH COLUMBIA

Thank you!

Any questions?