

Things that go BOOM!
**Common Dangerous
Drug Interactions**

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**Speaker has no
relationship to disclose.**

Objectives

- **Develop strategies for avoidance of dangerous drug interactions (30 mins)**
- **Identify 10 medication combinations that are involved in drug interactions (35 mins)**
- **Identify the most common CYP 450 drug interactions involving common medications (10 mins)**

Fluoroquinolones (FQ)

Fluoroquinolones approved by the FDA:

- [levofloxacin](#) (*Levaquin*),
- [ciprofloxacin](#) (*Cipro*), ciprofloxacin extended-release tablets,
- [moxifloxacin](#) (*Avelox*),
- [ofloxacin](#),
- [gemifloxacin](#) (*Factive*), and
- [delafloxacin](#) (*Baxdela*). There are more than 60 generic versions.

- Series of warnings over the last 10-11 years

BOOM!

FQ + Steroid

Combining FQs and Corticosteroids

- FQ alone: Risk of tendon rupture
- Steroid alone=> 3 fold increase in tendon rupture
- FQ plus steroid=> 43 fold greater risk of Achilles tendon rupture

Horn JR, Hansten PD. Fluoroquinolones and steroids: an Achilles heel interaction. *Pharmacy Times*. April 11, 2016. Source Accessed July 9, 2018.

Combining FQ and Corticosteroids

- Elderly patients with renal insufficiency, other risk factors
- Discuss possible complication with patient
- Monitor carefully for symptoms, stop immediately!

Horn JR, Hansten PD. Fluoroquinolones and steroids: an Achilles heel interaction. Pharmacy Times. April 11, 2016. Source Accessed July 9, 2018.

SSRIs/SNRIs

Serotonin, Serotonin, and more Serotonin

SSRIs/SNRIs

Serotonin, Serotonin, and more Serotonin

SSRIs (Serotonin-Reuptake Inhibitors)	SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors)
Escitalopram (Lexapro)	Duloxetine (Cymbalta)
Citalopram (Celexa)	Venlafaxine (Effexor)
Fluoxetine (Prozac)	Levo milnacipran (Fetzima)
Fluvoxamine (Luvox)	Desvenlafaxine (Pristiq)
Paroxetine (Paxil)	Venlafaxine (Effexor)
Sertraline (Zoloft)	

TCAs, “Other”

Serotonin, Serotonin, and more Serotonin

Tricyclic Antidepressants	“Other”
Amitriptyline (Elavil)	Trazodone (Oleptro)
Desipramine (Norpramin)	Mirtazapine (Remeron)
Doxepin	Vilazodone (Viibryd)
Nortriptyline (Pamelor)	Nefazodone (Serzone)
Anafranil (Clomipramine)	Vortioxetine (Trintellix)
Imipramine (Tofranil)	
Protriptyline (Vivactil)	

Quiz
What common medication used to treat depressive disorder, ADHD, and seasonal affective disorder hasn't been mentioned?
Why NOT?

Serotonin Syndrome

- Occurs when central and peripheral 5HT-1A and 5HT-2A receptors are overstimulated

Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. Ochsner J. 2013;13:533-540.

BOOM!

**2 or more
serotonergic
meds**

Serotonin Syndrome

***Why does this occur?
2 or more serotonergic drugs
interact with each other***

Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. Ochsner J. 2013;13:533-540.

**Manifestations of
Serotonin Syndrome**

- **Autonomic changes:** diarrhea, fever, flushing, hypo/hypertension, sweating
- **Neuromuscular changes:** hyperreflexia, increased muscle tone, restlessness, rigidity, tremor, shivering
- **Central Nervous system:** Agitation, confusion, delirium, hallucinations

Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. Ochsner J. 2013;13:533-540.

What Medication Combos? SSRI/SNRI *plus*:

- Tryptophan (OTC)
- Dextromethorphan (DM), codeine, TCAs, St. John's wort, tramadol
- Linezolid
- Meperidine, ecstasy, mirtazapine
- Buspirone, LSD, metoclopramide, triptans

By What Mechanism?

- *Increased serotonin production:* Tryptophan
- *Inhibition of serotonin reuptake:* DM, TCAs, St. John's wort, tramadol
- *Inhibition of serotonin metabolism:* Linezolid
- *Increased serotonin release:* DM, meperidine, ecstasy, mirtazapine
- *Stimulation of serotonin receptors:* Buspirone, LSD, metoclopramide, triptans

Serotonin Syndrome

- Usually within 6 hours of ingestion of the offending substance

Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. Ochsner J. 2013;13:533-540.

Quiz:
Patient takes sertraline (or your fave SSRI) daily for depression. She has migraine headaches. May a triptan be safely prescribed for her?

What about SSRIs/SNRIs plus Triptans?

- **Weigh risk/benefit but evidence does not support avoidance of triptans (if this is the only serotonergic med she takes)**
- **Monitor!**

vans RW, Tepper SJ, Shapiro RE, Sun-Edelstein C, Tietjen GE. The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. Headache. 2010;50:1089-1099.

Quiz:
A 42 year old male patient has had 3 back surgeries and has chronic low back pain. He takes 60 mg duloxetine daily, 50 mg amitriptyline HS, gabapentin 300 mg TID and tramadol 100 mg (with 650 mg acetaminophen) 1-3 times daily PRN pain. When he is unable to sleep, he takes trazodone 25 mg HS. He has zolpidem (Ambien) 5 mg for sleep if trazodone doesn't help. What's a likely potential problem?

Medication Assessment

Medication	Effect on Serotonin
Gabapentin	None
Acetaminophen	None
Zolpidem	None
Amitriptyline 50 mg HS	Inhibit serotonin reuptake
Trazodone 25 mg HS	Inhibit serotonin reuptake
Tramadol 100 mg-300 mg	Inhibit serotonin reuptake
Duloxetine 60 mg daily	Inhibit serotonin reuptake

If he's not having problems now, he is very likely to have one soon!

How could you manage this to decrease likelihood of serotonin syndrome?

*Prescriber Strategy 1: Decrease serotonin load!
Can we decrease or stop a med? Which one?*

Medication	Effect on Serotonin
Gabapentin	None
Acetaminophen	None
Zolpidem	None
Amitriptyline 50 mg HS	Inhibit serotonin reuptake
Trazodone 25 mg HS	Inhibit serotonin reuptake
Tramadol 100 mg-300 mg	Inhibit serotonin reuptake
Duloxetine 60 mg daily	Inhibit serotonin reuptake

How could you manage this to decrease likelihood of serotonin syndrome?

*Strategy 2: Patient education!
No OTCs without checking with pharmacist!
Do not exceed dose of ANY medication!!!!*

Medication	Effect on Serotonin
Gabapentin	None
Acetaminophen	None
Zolpidem	None
Amitriptyline 50 mg HS	Inhibit serotonin reuptake
Trazodone 25 mg HS	Inhibit serotonin reuptake
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Suppose he develops a cough and asks about Robitussin DM (dextromethorphan)?
What med could he safely receive for cough?

Take Home Point!

*Serotonin Syndrome is real and there's no lab test to identify it.
Must have an index of suspicion!*

St. John's Wort

St. John's Wort *Hypericum perforatum*

- Antidepressant, antianxiety properties
- **3A4 inducer** (causes certain drugs to be metabolized more rapidly)

Borrelli F, Izzo AA. Herb-drug interactions with St John's wort (*Hypericum perforatum*): an update on clinical observations. *AAPS J.* 2009;11:710-727.

CYP 3A4 Enzymes

- CYP450 enzyme system
- 3A4 metabolizes about 50% of all clinically useful medications
- Most abundant and clinically significant
- Actually composed of 4 enzymes:
3A3, 3A4, 3A5, 3A7

3A

When a substance is an "Inducer"

- Speeds up metabolism of the drug
- Decreases affect of drugs (usually)

Here's what happens during *induction*

Clinical Example 1:
St. John's wort - Inducer
Patient is on indinavir (Crixivan). He begins to take St. John's wort for depression.
Potential problem: Increased viral load.
Reason: St. John's wort is 3A4 inducer and causes reduced efficacy of indinavir due to rapid metabolism.

St. John's Wort
(3A4 inducer)

The diagram illustrates the interaction between St. John's Wort and two drugs. St. John's Wort is labeled as a 3A4 inducer. It is shown with an arrow pointing to Indinavir and Cyclosporin, both of which are also labeled as 3A4 substrates. This interaction results in an **Increased viral load**.

Blank box for notes.

Clinical Example 2:
St. John's wort - Inducer

Patient had a kidney transplant and takes cyclosporine. He starts taking St. John's wort for depression.

Potential problem: Transplant rejection.

Reason: St. John's wort is 3A4 inducer and causes rapid metabolism of cyclosporine. Antirejection properties are diminished.

St. John's Wort (3A4 inducer)

Cyclosporine $\xrightarrow{3A4}$ **Organ Rejection**

St. John's Wort *Hypericum perforatum*

St. John's Wort *Hypericum perforatum*

- Hyperforin is bioactive component of St. John's wort
- Hyperforin probably responsible for antidepressant/antianxiety properties **AND INDUCTION of 3A4/3A5 enzymes**

Borrelli F, Izzo AA. Herb-drug interactions with St John's wort (*Hypericum perforatum*): an update on clinical observations. AAPS J. 2009;11:710-727.

“Statins”

- **1 in 4 Americans age 40 and older use statins**

Statins

- The risk of serious **muscle injury, including rhabdomyolysis**, due to statin use is **< 0.1%**
- The risk of statin-induced serious **hepatotoxicity** is approximately **0.001%**
- The risk of **newly diagnosed diabetes** caused by statin use is approximately **0.2%** per year of treatment and can vary based on underlying diabetes risk in certain populations

Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association [Published online December 10, 2018]. *Arterioscler Thromb Vasc Biol*. doi:10.1161/ATV.0000000000000073.

**Statins....
Statin toxicity
including rhabdo**

Statins

- Many drug drug interactions (DDIs) related to CYP450 (except pravastatin)
- CYP3A4 and CYP2C9 enzymes involved

Wiggins BS, Saseen JJ, Lee R, et al. Recommendations for management of clinically significant drug-drug interactions with statins and selective agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. Published online October 17, 2016. <http://circ.ahajournals.org/content/early/2016/10/17/CIR.0000000000000456>. Accessed February 25, 2017.

Statins *plus* Gemfibrozil

- Gemfibrozil used to treat mixed dyslipidemia and hypertriglyceridemia, type IV, V

Statins *plus* Gemfibrozil

Muscle TOXICITY!!!

Statins *plus* Gemfibrozil

- **Increases concentration of statins; Do not use in combo!!!**
- **Muscle TOXICITY!!!**
- **Rosuvastatin concentration increased 56% - 88%**
- **Pravastatin increased > 100%**

Wiggins BS, Saseen JJ, Lee R, et al. Recommendations for management of clinically significant drug-drug interactions with statins and selective agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. Published online October 17, 2016. <http://circ.ahajournals.org/content/early/2016/10/17/CIR.0000000000000456>. Accessed February 25, 2017.

Quiz:

Patient takes pravastatin (for LDL elevation) and has triglyceride levels >700. What fibrate may be safely prescribed for her elevated triglycerides?

Best Answer:

Fenofibrate!

(FYI: If gemfibrozil MUST be used, the authors preferred atorvastatin, pitavastatin, rosuvastatin, or fluvastatin.)

Wiggins BS, Saseen JJ, Lee R, et al. Recommendations for management of clinically significant drug-drug interactions with statins and selective agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. Published online October 17, 2016. <http://circ.ahajournals.org/content/early/2016/10/17/CIR.0000000000000456>. Accessed February 25, 2017.

What about Calcium Channel Blockers and Statins?

Calcium Channel Blockers

Decrease BP
DHPs

- **Norvasc** (amlodipine)
- **Procardia** (nifedipine)
- **Plendil** (felodipine)
- **Dynacirc** (isradipine)
- **Cardene** (nicardipine)

Decrease HR
Non-DHPs

- **Cardizem, Tiazac** (Diltiazem)
- **Calan, Covera HS, Verelan** (verapamil)

Non-DHPs decrease Heart Rate (and BP a little)

Quiz: Any worries about prescribing amlodipine *plus*:

- Simvastatin?**
- Lovastatin?**
- Rosuvastatin?**
- Pravastatin?**
- Pitavastatin?**
- Atorvastatin?**

Quiz: What clinical problem is likely with amlodipine *plus*:

**Simvastatin?
Lovastatin?**

Don't exceed 20 mg of Simva/Lova if concomitant amlodipine.

Wiggins BS, Saseen JJ, Lee R, et al. Recommendations for management of clinically significant drug-drug interactions with statins and selective agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. Published online October 17, 2016. <http://circ.ahajournals.org/lookup/early/2016/10/17/CIR.0000000000000456>. Accessed February 25, 2017.

Quiz: Any worries about prescribing diltiazem *plus*:

**Simvastatin?
Lovastatin?
Atorvastatin?**

Quiz: Any worries about prescribing diltiazem *plus*:

**Simvastatin? (don't exceed 10 mg)
Lovastatin? (don't exceed 20 mg)
AHA: "avoid Simva/Lova with diltiazem or verapamil"**

**Atorvastatin? (minor increase)
AHA: "monitor"**

Wiggins BS, Saseen JJ, Lee R, et al. Recommendations for management of clinically significant drug-drug interactions with statins and selective agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. Published online October 17, 2016. <http://circ.ahajournals.org/lookup/early/2016/10/17/CIR.0000000000000456>. Accessed February 25, 2017.

**What about
Calcium Channel
Blockers and
Macrolides?**

Statins plus Macrolide antibiotics?

Which one is safest?

- 1. Azithromycin**
- 2. Erythromycin**
- 3. Clarithromycin**

**What about
Digoxin and
Statins?**

Digoxin *plus* Statins?

Not usually any worries about increased digoxin levels.
Exception: High doses of atorvastatin

Wiggins BS, Sareen JJ, Lee R, et al. Recommendations for management of clinically significant drug-drug interactions with statins and selective agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. Published online October 17, 2016. <http://circ.ahajournals.org/content/early/2016/10/17/CIR.0000000000000456>. Accessed February 25, 2017.

BOOM!

Statins *plus*:

- Gemfibrozil
- Some CCBs
- Maybe Digoxin

Other Medications *plus* Statins?

More Problems: Other Medications *plus* Statins?

- **ANTIFUNGALS!**
- **Amiodarone (Cordarone)**
- **Dronedarone (Multaq)**
- **Warfarin (any statin-check INR after starting)**
- **Ticagrelor (Brilinta)**
- **Immunosuppressants**
- **Colchicine**

Wiggins BS, Sareen JJ, Lee R, et al. Recommendations for management of clinically significant drug-drug interactions with statins and selective agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. Published online October 17, 2016. <http://circ.ahajournals.org/content/early/2016/10/17/CIR.0000000000000456>. Accessed February 25, 2017.

Take Home Point:

- **Many medication issues with statins**
- **Too many to remember**
- **Check for drug interactions**

Take Home Point: Statins with *fewest* CYP 450 drug interactions:

- **Pravastatin**
- **Rosuvastatin**

Take Home Point:

Statins with *most* CYP 450 drug interactions

- Simvastatin
- Lovastatin

ACEs and ARBs

**TMP/SMX
Drug Interactions**

- Possible **HYPERKALEMIA** when TMP-SMX combined with meds that increase potassium
- ACEs, ARBs, potassium sparing diuretics, NSAIDs

Prescribers Letter; January 2015; Vol 31
Paauw DS. Hyperkalemia: the riskiest drugs. Medscape Internal Medicine. September 3, 2015. <http://www.medscape.com/viewarticle/850360> Accessed January 5, 2019.

TMP/SMX Drug Interactions

- Trimethoprim decreases excretion of potassium (acts on the distal nephron, blocking the epithelium Na channel which leads to reduction in renal excretion of K)
- Hyperkalemia develops 4-5 days after taking TMP/SMX, so 3 day dose likely OK

Prescribers Letter; January 2015; Vol 31
Paauw DS. Hyperkalemia: the riskiest drugs. Medscape Internal Medicine. September 3, 2015. <http://www.medscape.com/viewarticle/850360> Accessed January 5, 2019.

TMP/SMX Drug Interactions

- 81.5% had significant increase in serum K from baseline
- 18% had hyperkalemia > 5 meq/L
- 6% had hyperkalemia > 5.5 meq/L
- Reversible once TMP/SMX is d/c'd

Alappan R, Buller GK, Perazella MA. Trimethoprim-sulfamethoxazole therapy in outpatients: is hyperkalemia a significant problem? *Am J Nephrol* 1999;19:389-94.

Drug Interactions

- 6% of patients on TMP/SMX develop hyperkalemia
- Hospitalizations increase 7-fold when elders take TMP-SMX with ACE, ARB, etc
- Even higher when combined in patients who take ACEs, ARBs, or spironolactone

Prescribers Letter; January 2015; Vol 31
Paauw DS. Hyperkalemia: the riskiest drugs. Medscape Internal Medicine. September 3, 2015. <http://www.medscape.com/viewarticle/850360> Accessed January 5, 2019.

EXTRA Care in These Patients!

- Elderly
- Renal insufficiency
- DM
- Heart failure

***If no alternative to TMP/SMX, check K level after day 3

Prescribers Letter; January 2015; Vol 31
Pauw DS. Hyperkalemia: the riskiest drugs. Medscape Internal Medicine. September 3, 2015. <http://www.medscape.com/viewarticle/850360> Accessed January 5, 2019.

BOOM!

**ACE/ARB plus
TMPS**

**What about other
Antibiotics and
hyperkalemia?**

What about other Antibiotics and hyperkalemia?

Safe!

- Amoxicillin
- Nitrofurantoin
- Ciprofloxacin
- Norfloxacin

While we're talking about antibiotics...

QT interval prolongation

- Azithromycin
- Quinolones

Ball P. Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. *J Antimicrob Chemother.* 2000;45:557-559. <http://jac.oxfordjournals.org/content/45/5/557.full> Accessed January 5, 2019.
Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med.* 2012;366:1881-1890. [Abstract](#)

...back to the ACEs and ARBs

Triple Whammy= 31% higher risk of acute kidney injury

ACE or ARB plus diuretic plus NSAID or Aspirin

Triple Whammy

- **ACE/ARB**: reduce glomerular filtration pressure via vasodilation of the efferent arteriole
 - **NSAID/ASA**: inhibits renal prostaglandin synthesis (inhibits dilation of renal arteries and decreases blood flow to the glomerulus)
 - **Diuretics** decrease intravascular volume and reduce blood flow to the glomerulus
- The combo leads to reduction in renal blood flow and renal dysfunction

Triple Whammy

ACE-I dilates, filtration pressure decreases

NSAIDs reduce blood flow to the glomerulus

Diuretics reduce blood flow (reduce intravascular volume)

Community Acquired- Acute Kidney Injury (AKI)

- Study: 78,000 patients
- AKI defined as 1.5 fold or more above baseline
- RAS or diuretic increased risk, no NSAIDs
- RAS plus diuretic 2x risk, no NSAIDs
- Greatest risk: loop diuretic, RAS inhibitor, and aldosterone antagonist diuretic, no NSAIDs
- Risk highest in patients > 75 y/o or existing kidney disease

Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney Int. 2015 Apr 15.

Community Acquired- Acute Kidney Injury (AKI) When NSAID added

Community Acquired- Acute Kidney Injury (AKI)

When NSAID added:

- 66% increased risk of AKI
- Highest risk: NSAID, ACE/ARB, loop diuretic, and aldosterone antagonists
- When AKI developed: 10x risk of hospitalization, 4-5x risk of death

Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney Int. 2015 Apr 15.

Highest Risk for the Triple Whammy?

- Especially deleterious in elderly patients, diabetics, renal insufficiency, ascites, or HF (“double whammy” can cause acute injury)
- During first few months of therapy

Horn JR, Hansten PD. Diuretics, ACEIs, ARBs, and NSAIDs: a nephrotoxic combination. Pharmacy Times. April 18, 2013. Accessed January 10, 2019.

Protection from the Triple Whammy

- Keep well hydrated
- Monitor BP and serum Cr for first few months
- NSAID use: 6-12 hour (not 24 hours)
- Avoid NSAID, use tramadol, acetaminophen instead, other modality

Teaching Point

- Stop diuretic (and NSAID) if at risk for volume depletion (diarrhea, vomiting, unable to drink, etc.)

NSAIDs

Triple Whammy= risk of acute kidney injury

ACE or ARB plus diuretic plus NSAID

Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int.* 2015 Apr 15.

NSAIDs

- **Cause sodium and water retention so blunt the effect of most antihypertensive agents**

NSAIDs blunt effects of antihypertensive meds.
Which agent has the least effect on BP?
1. ACEs
2. ARBs
3. CCBs
4. Diuretics

Prohypertensive Effect
• NSAID is dose dependent
• Involves COX-2 in kidneys: reduces sodium excretion, increases intravascular volume

BOOM!
NSAIDs plus Anti-hypertensives

What is the most commonly dispensed medication in the US?

TOP 20 Dispensed Rx's

Medication	Medication
1. Levothyroxine	11. Amoxicillin
2. Acetaminophen/hydrocodone	12. Fluticasone
3. Lisinopril	13. Gabapentin
4. Metoprolol	14. Alprazolam
5. Atorvastatin	15. Hydrochlorothiazide
6. Amlodipine	16. Azithromycin
7. Metformin	17. Furosemide
8. Omeprazole	18. Sertraline
9. Simvastatin	19. Tramadol
10. Albuterol	20. Losartan

Synthroid (levothyroxine)

- 2-5/100 patients has hypothyroidism
- Thyroid supplement for patients with hypothyroidism (T₄)
- Enhance oxygen consumption by most tissues in the body and **increase metabolic rate and metabolism of carbs, protein, and lipids**

Synthroid (levothyroxine)

- T₄ absorbed in the small bowel when taken orally
- Absorption varies from 40-80%
- Prefer daily oral dose, empty stomach, 30 minutes before food is eaten
- Fasting increases absorption of T₄

What else effects absorption of levothyroxine besides food?

PPIs plus Levothyroxine

PPIs

- Dexlansoprazole (Dexilant)
- Esomeprazole (Nexium)
- Lansoprazole (Prevacid)
- Omeprazole (Prilosec)
- Pantoprazole (Protonix)
- Rabeprazole (Aciphex)

Quiz: Patient who has hypothyroidism takes levothyroxine (TSH = 2.5). She starts an OTC PPI. What is likely to happen to her TSH?

1. It will increase
2. It will decrease
3. It will stay the same
4. I don't have a clue

Levothyroxine plus PPIs

- More levothyroxine may be needed when patients are on acid suppressing medications
- A median increase in TSH of .12 mU/L
- Levothyroxine better absorbed in an acidic environment

Irving SA, Vadeloo T, Leese GP. Drugs that interact with levothyroxine: an observational study from the Thyroid Epidemiology, Audit and Research Study (TEARS). Clin Endocrinol (Oxf). 2015;82:136-141.
Bolk N, Visser TJ, Nijman J, et al. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. Arch Intern Med 2010;170:1996-2003.

Effects of Food/Meds

Interacting Substance	Comments
H2 blockers, PPIs	Median decrease in TSH of 0.12 mU/L
Calcium Salts	Decreases absorption about 20%; median TSH increase 0.27 mU/L
Coffee, espresso	Reduces absorption about one-third (wait an hour but at least 30 mins)
Iron salts	Median increase in TSH 0.22 mU/L
Statins	Median decrease in TSH 0.17 mU/L; mechanism unknown

Prescribers letter 2015; 22(4):310420
 Jonkass J, Blanco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism. *Thyroid* 2014;24:1670-751.
 Irving SA, Vadeloo T, Leese GP. Drugs that interact with levothyroxine: an observational study from the Thyroid Epidemiology, Audit and Research Study (TEARS). *Clin Endocrinol* 2015;82:136-41.

Levothyroxine: Decreased Absorption with Other Meds

- Aluminum hydroxide
- Bile acid sequestrants
- Iron salts
- Estrogen
- Magnesium salts
- Orlistat (Xenical)
- Simethicone
- Soy
- Sucralfate (Carafate)

Irving SA, Vadeloo T, Leese GP. Drugs that interact with levothyroxine: an observational study from the Thyroid Epidemiology, Audit and Research Study (TEARS). *Clin Endocrinol (Oxf)*. 2015;82:136-141.

Bolk N, Visser TJ, Nijman J, et al. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. *Arch Intern Med* 2010;170:1996-2003.

BOOM!

Levothyroxine plus Almost anything!!!

Take Home Point

- If euthyroid patient starts/stops acid suppression therapy, check TSH in 4-8 weeks
- Remind patient to let you know if taking OTC meds

Anticoagulants

- Warfarin
- Direct oral anticoagulants (DOACs)

Warfarin and Antimicrobials

Quiz: Patient takes warfarin therapy. Stable INR. She develops a UTI and is given TMP/SMX. What is likely to happen to her INR?

- 1. It will increase**
- 2. It will decrease**
- 3. It will stay the same**
- 4. I don't have a clue**

TMP/SMX

- Raise INR and increase bleeding risk 2-4 fold; especially in older patients**
- Consider alternative**

Mechanism of Action with TMP/SMX

- Displacement of warfarin from protein binding sites**
- Alterations in gut flora**
- Increased INR seen with 3 day course of TMP/SMX**

Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: practice tool and practical management tips. *CPJ/RPC* 2011;144:21-34.

Quiz: 60 y/o female takes warfarin therapy. Stable INR.

**She develops a UTI.
What is a prudent choice of antibiotics to treat her UTI?**

- 1. 3 days of ciprofloxacin**
- 2. 7 days of ciprofloxacin**
- 3. Nitrofurantoin 5 days**
- 4. 3 days of TMP/SMX**

Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: practice tool and practical management tips. *CPJ/RPC* 2011;144:21-34.

Quiz: 70 y/o male takes warfarin therapy. Stable INR.

**He has diarrhea secondary to *C. difficile*.
Is metronidazole a good choice to treat his *C. diff*?**

Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: practice tool and practical management tips. *CPJ/RPC* 2011;144:21-34.

What do we know?

- Metronidazole will raise INR and increase bleeding risk 2-4 fold; especially in older patients**
- Consider alternative**

Mechanism of Action: Oral Metronidazole

- Inhibits metabolism of warfarin
- Topical preparations associated with less systemic absorption so, less likely to increase INR

Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: practice tool and practical management tips. *CPI/RPC* 2011;144:21-34.

TMP/SMX or Metronidazole

- IF no alternative: consider empirically lowering the warfarin dose 25%-40% if at high risk of bleed

Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: practice tool and practical management tips. *CPI/RPC* 2011;144:21-34.

Take Home Point

Generally speaking

- Monitor INR about 5 days after starting drug, then when drug is stopped
- **EXCEPTION: Rifampin**

Rifampin

- Can decrease INR
- May take several weeks to see full effect
- Check INR for several weeks after starting rifampin
- Consider increasing warfarin dose by 25%-50%

Take Home Point

- Oral cephalosporins (cefaclor, cefixime, cefpodoxime, cefuroxime) **NOT** been shown to interact with warfarin
- Oral penicillin G, ampicillin probably do not interact

Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005;165:1095-106.

Is Acetaminophen safer in combo with Warfarin?

Take Home Point

- Regular use of acetaminophen will increase INR
- Check INR after 3-5 days of acetaminophen use
- Not necessary for occasional use

Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005;165:1095-106.

Mechanism of Action Acetaminophen

- Hepatic metabolism of warfarin is inhibited

Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: practice tool and practical management tips. *CPI/RPC* 2011;144:21-34.

BOOM!

Warfarin *plus*

1. TMP/SMX, others
2. Acetaminophen
3. Prednisone
4. Statins (simvastatin: decrease warfarin by 1 mg)
5. Omeprazole

Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005;165:1095-106.

Anticoagulants

- Direct oral anticoagulants (DOACs)

DOACs

Direct Xa inhibitor: inhibits factor Xa in coagulation cascade

- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)

DOACs

Direct Thrombin Inhibitor: inhibits the enzyme, thrombin

- Dabigatran (Pradaxa)

Direct Xa Interactions (3A4, P-glycoprotein inh)

Rivaroxaban, Apixaban	Risk of Bleeding
Clarithromycin, erythromycin	Increase
Ketoconazole	Increase
Ritonavir	Increase
Amiodarone	Increase
Others	

Direct thrombin Inhibitor Interactions (P- glycoprotein inh)

Dabigatran	Risk of Bleeding
Ketoconazole	Increase
Quinidine	Increase
Amiodarone	Increase
Others	

BOOM!

Amiodarone *plus* DOACs

- Amiodarone used to treat a-fib
- DOACs used to treat a-fib

Grapefruit and the 3A4 substrates

CYP 3A4 Substrates

- A medication that requires 3A4 enzymes to metabolize it is known as a 3A4 substrate

3A4

CYP 3A4 Enzymes

- These liver enzymes metabolize 3A4 substrates

3A4

CYP 3A4 Inhibitor

- Medication or substance that prevents the 3A4 enzymes from metabolizing 3A4 substrates

3A4

Don't mix substrates and Inhibitors!

3A4 Substrate	3A4 Inhibitors
Ondansetron (Zofran)	Clarithromycin (Strong)
Clarithromycin, erythromycin	Ketoconazole (Strong)
Dextromethorphan	Many protease inhibitors (Strong)
Most calcium channel blockers	Erythromycin (Intermediate)
Atorvastatin, lovastatin, simvastatin	Grapefruit juice (Intermediate)
Cyclosporin	Verapamil, diltiazem (Intermediate)
Many benzos	Cimetidine (Weak)
Salmeterol	Ciprofloxacin (Possible)
Cocaine	

Mayomedicallaboratories.com; Curr Drug Metab. 2008 May;9(4):310-22; www.fda.gov

Take Home Point:
Combining Substrates with their Inhibitors is NEVER a good idea!!!

BOOM!

**3A4 Substrates *plus*
3A4 Inhibitors**

Take Home Point:

- Too many to remember
- Always check for drug interactions

The 7 Sins!

1. St. John's Wort
2. SSRIs, SNRIs
3. Statins
4. ACEs/ARBs
5. PPIs
6. Warfarin
7. TMP/SMX

Top 10 CYP450 Drugs
to watch out for!

10. Ciprofloxacin
9. Cimetidine
8. Warfarin
7. Erythro/clarithro
6. Ketoconazole

Top 10 Drugs
to watch out for!

5. Bactrim
4. Paroxetine & Fluoxetine
3. Phenytoin
2. Levothyroxine
1. Atorvastatin/Simvastatin

Thank you!

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