# Common Drug Interactions and Side Effects

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# Disclosure of Financial Relationships

## Douglas Paauw

Has no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

# Problems With PPI's?

- Decreased Ca absorption
- Decreased iron absorption
- Increased fracture risk
- Decreased thyroid absorption
- Poor Magnesium absorption
- Poor B12 absorption
- Decreased Ketoconazole/Itraconazole absorption
- Decreased Atazanavir absorption
- Increased risk of C. difficile, and recurrent C Diff and more severe C diff. FDA warning 2/12
- Acute an chronic kidney disease

- 1) Pharmacist calls to tell you that you are prescribing a triptan for a patient who is on an SSRI (citalopram 20 mg a day). She is on no other meds. What should you do?

A) Switch to another migraine treatment

B) Have patient not take citalopram for 24 hours after taking the triptan

C) Cut the dose of triptan by 50 %

D) Don’t worry

# Triptans and SSRI's

- Concern for serotonergic syndrome
- Extremely unlikely if only a triptan + SSRI (especially at lower doses of SSRI)
- Beware of patients on multiple drugs that can trigger serotonergic syndrome ( tramadol, linezolid,meperidine, dextromethorphan, TCA, MAOI, buspirone, trazadone)

- 2) A 18 yo woman is brought to the ED after attending a party. She is confused, and has been vomiting. On exam, T 39, P 130, BP 170/100. She is diaphoretc. She has tremors and is hyperreflexic. She had been feeling fine earlier in the day. Current medications : Ranitidine, Vitamin D, Escitalopram and ethinyl estradiol/northethindrone. What is the most likely cause of her symptoms?
- A) Cocaine/ Ranitidine interaction
- B) Cocaine/ Ethinyl Estradiol interaction
- C) Alcohol/ Ranitidine/Escitalopram interaction
- D) Ecstasy/Escitalopram interaction
- E) Ecstasy/ Alcohol/ethinyl estradiol interaction

# Drugs of Abuse and Serotonin Syndrome

- Adding any of the following to SSRI's can provoke serotonin syndrome
- Cocaine
- High dose dextromethorphan
- Ecstasy and other amphetamines
- Tramadol
- Bath Salts
- J Clin Psychiatry. 2012 Aug;73(8):1126-7.
- Int J Adolesc Med Health. 2013;25(3):193-9.

# Warfarin Interactions

3) A 72 y.o. male S/P AVR replacement two years ago for aortic stenosis presents with wide spread bruising on his back/legs and some bruising on the back of both hands. His last INR was three weeks ago and was 3.0. He states he saw an M.D. six days ago for a cough and was put on a medication described as a “white tablet.” His chronic medications include: Coumadin 5 mg qd, Albuterol inhaler 2 puffs 4 times a day and Nortryptiline 25 mg qhs.

## What medication was he placed on?

a) Amoxicillin

b) Codeine

c) Cefixime

d) Azithromycin

e) TMP/Sulfa

# Warfarin Interactions
## Decrease metabolism (increase PT)

| Most Severe | Possible* |
| --- | --- |
| TMP/Sulfa | Quinolones |
| Erythromycin | Omeprazole |
| Amiodarone | Clarithromycin |
| Propafenone | Azithromycin |
| Ketoconazole/fluconazole | |
| Itraconazole | |
| Metronidazole | * Especially in elderly and polypharmacy |

# Antibiotics and Warfarin

- Retrospective cohort study 104 patients on stable warfarin therapy. Effect on INR of Terazocin (control), Azithromycin (32 patients), Levofloxacin (27) and TMP/Sulfa (16)
- Mean change in INR: Terazocin -.15, Azithromycin + .51 , Levofloxacin + .85, TMP/Sulfa +1.76
- Percent patients having a INR > 4: Terazocin 5%, Azithromycin 31%, Levofloxacin 33%, TMP/Sulfa 69%
- JGIM 2005;20 (7);653-6.

# Antibiotics for UTI in Patients on Warfarin

- Penicillins/cephalosporins ok
- Nitrofurantion ok
- Quinolones- be worried
- TMP/Sulfa don’t use

4) A 39 y.o. woman with a prosthetic aortic valve presents with bruising. Her last INR 6 weeks ago was 2.4, today's INR is 6.5. She has not taken any extra Coumadin. Which of the following when taken on a daily basis could explain her increased INR?

a) Acetaminophen
b) Calcium carbonate
c) OCP
d) Ranitidine
e) DOSS

# Warfarin and Acetaminophen

- 3 studies suggest increased INR with Acetaminophen + Warfarin
- > 9100 mg/week led to 10 x risk of having INR > 6*
- In double blind crossover trial patients on Warfarin + 4 g/d of Acetaminophen had PT 1.75 X control [+]
- Patients received 2 gm or 4 gm acetaminophen or placebo with warfarin, 54% of those receiving acetaminophen overshot INR goal vs 17% of placebo #.

*JAMA 1998;279:657-662

[+] Clin Res 1984;32:698a

# Pharmacotherapy 2007; 27 (5):675-83.

- 5) A 76 yo man is admitted with increasing SOB. He has a long history of COPD and has had a recent productive cough. He is admitted to the hospital and treated with amoxicillin, prednisone, codeine, and albuterol. PMH: A fib, Hypertension, COPD, GERD. Outpatient meds: Metoprolol, coumadin, pantoprazole, lisinopril. His recent INR 2 weeks ago was 2.2, on hospital day 6 it is 4.3. What is the most likely interaction with coumadin?
- A) Prednisone
- B) Amoxicillin
- C) Codeine
- D) Amoxicillin + Pantoprazole

# Effect of Oral Corticosteroids On Warfarin Therapy

- Retrospective review of patients in ACC who received oral corticosteroids. Patients were excluded if they were treated with any drug with a known interaction with warfarin.
- Mean difference between pre steroid INR and the INR when patients on steroids was 1.24, $p<.001$. 62% of the patients had an INR above their targeted range. Mean time to INR elevation was 6.7 days after starting steroids.
- Ann Pharmacother 2006;40:2101-6.

# Problems with Statins

- 6) A 65 yo man presents with cough and fever. He has had severe diarrhea for 2 days. He was on a cruise with a friend who was diagnosed with Legionella yesterday. PMH – diabetes, hyperlipidemia,hypertension. Meds: Lisinopril, simvastatin, amlodipine, gemfibrozil,metformin. Chest Xray shows patchy bilateral infiltrates. WBC 17,000 Na 125. What is the most appropriate treatment?

A)Amoxicillin/clavulanate

B)Clarithromycin

C)Levofloxacin

D)Cefuroxime

E)Trimethoprim/sulfa

# Drugs That Increase Risk of Statin Toxicity

- Fibrates (Gemfibrozil 15X >> Fenofibrate)
- Azole antifungals
- Amiodarone
- Erythromycin/Clarithromycin
- Protease inhibitors
- Verapamil/Diltiazem
- Least drug interactions with pravastatin, most with simvastatin and lovastatin

# How to Minimize Danger?

- Avoid simvastatin if you can
- No concurrent dosing
- If drug interactions likely use pravastatin or rosuvastatin

# Side Effects of Statins

- Rhabdomyolysis (rare) 0.01%
- Hepatotoxicity (rare)
- Liver failure 0.0001%
- Myalgias 5-18 %

# What Should You Worry About When Prescribing Simvastatin?

- Major interaction with grapefruit juice
- Mild interaction with warfarin
- Major interaction with amiodarone
- Usual statin concern with fibrates/clarithromycin/azoles
- Red flags should go off when prescribing for A fib patients, where they might be on both warfarin and amiodarone (and a Ca channel blocker)
- June 2011 FDA advisory to not put new patients on 80mg of simvastatin

- Florentin M. Expert Opin Drug Saf. 2012 May;11(3):439-44.

- 8) A 70 yo man presents with nausea and weakness. He has a history of CAD, HTN and depression. He was seen 1 week ago for nausea and abdominal pain and was started on treatment for ulcer disease with H pylori. Meds: asa,nifedipine, omeprazole,amoxicillin,fluoxetine, clarithromycin.
- PE: Vs BP 90/60 p 100
- Labs: Bun 35 Cr 3.8 K 4.8
- What is the most likely cause of the patients renal insufficiency?
- A) Allergic interstitial nephritis
- B) Pravastatin- clarithromycin interaction
- C) Pravastatin- nifedipine interaction
- D) Nifedipine- clarithromycin interaction

# Hypotension and ARI from Clarithromycin – Dihydropyridine Interaction

- Retrospective cohort study in Ontario, Canada, from 2003 through 2012 of older adults (mean age, 76 years) who were newly coprescribed clarithromycin (n = 96,226) or azithromycin (n = 94,083) while taking a calcium-channel blocker (amlodipine, felodipine, nifedipine, diltiazem, or verapamil).
- Coprescribing clarithromycin vs azithromycin with a calcium-channel blocker was associated with a higher risk of hospitalization with acute kidney injury ( odds ratio [OR], 1.98 [95% CI, 1.68-2.34]).
- The risk was highest with dihydropyridines, particularly nifedipine (OR, 5.33 [95% CI, 3.39-8.38 )

- JAMA. 2013 Dec 18;310(23):2544-53.

# Hypotension Related to Macrolide-Calcium Channel Blocker Interaction

- Nested, case-crossover study of patients age 66 and older prescribed a CCB over a 15 year period.
- Study group was those admitted to the hospital with hypotension/shock
- Compared risk of exposure to macrolide in 7 days before hospitalization with 7 day control interval the month prior
- RR of hypotension 5.8 for erythromycin, 3.7 for clarithromycin. Azithromycin was not associated with hypotension
- CMAJ 2011;183 (3):303-307.

# Beware of Clarithromycin

- Major statin interaction (especially simvastatin/lovastatin)
- Major interaction with CCB
- Increase levels of glypizide/glyburide (hypoglycemia)
- Major interaction with colchicine
- 82 Major drug interactions reported!

# Important Drug Side Effects

- 9) A 78 yo man presents to his physician for evaluation of edema. He reports a 3 month history of bilateral peripheral edema. He has had no pain or SOB. PMH: Htn, parkinsons disease, depression and type 2 DM. Medications: Lisinopril, diltiazem, atorvastatin, pramipexole, escitalopram and metformin. Exam: BP 110/70, P 70 no increased JVP. Chest – clear. Ext- bilateral edema 2+
- What is the most likely cause?
- A) CHF
- B) Diltiazem
- C) Lisinopril
- D) Pramipexole
- E) Escitalopram

# Drug Induced Edema

- Dihydropyridines (nifedipine, felodipine, amlodipine)
- Pioglitazone
- NSAIDS
- Estrogen and testosterone
- Pramipexole
- Gabapentin and pregabalin (7-8%)
- Omeprazole

# Pramipexole Induced Peripheral Edema

- Retrospective case series
- 300 patients who received pramipexole
- 17 patients developed peripheral after starting pramipexole.
- Mean dose of pramipexole at onset of edema was 1.7 g a day
- All patients edema resolved when pramipexole was stopped, it recurred in every patient who had pramipexole restarted
- Arch Neurol. 2000 May;57(5):729-32.

- 10) A 60 yo man develops pain in his feet over the past week. He describes the pain as burning, and sharp. No swelling, or redness. PMH: alcoholism (quit drinking 3 years ago), hypertension, CAD, prostatitis, and diabetes. Meds: rosuvastatin, lisinopril, metformin, levofloxacin, amlodipine. Exam- hyperasthesia both feet. What do you recommend?
- A) Start B12 supplementation
- B) Stop Rosuvastatin
- C) Stop Metformin
- D) Stop Levofloxacin
- E) Stop Amlodipine

# Quinolones and Peripheral Neuropathy

- Known since 1990's
- Can occur within 1st 24 hours on medication, most within 1 week
- Parasthesia most common intitial symptom (81%)
- FDA clarified this concern 8/2013

J Antimicrob Chemother. 1996 Apr;37(4):831-7

Ann Pharmacother. 2001 Dec;35(12):1540-7

# Risk of Tendonopathy With Quinolones

- Large healthcare database of achilles tendonitis and rupture reviewed for risk factors
- Charts were reviewed for antibiotic use in the previous 30 days, compared to control patients. Also evaluated for risk of steroid use, BMI, diabetes and renal failure
- Quinolone antibiotics were associated with OR of 4.3 for achilles tendonitis and OR 2.0 for achilles rupture. Risk was 48/100,000 new quinolone  prescriptions for achilles tendonitis, 6/100,000 for achilles tendon rupture.
- Risk of Achilles tendonitis was higher in patients > 60 years of age (OR 8.3 vs 1.6 in patients < 60 years), BMI <30 (OR 7.7 vs 2.4 for BMI >30), and patients on glucocorticoids (OR 9.1 vs 3.2).
- AMJ 2012. Dec : 125

# Quinolones and Tendon Rupture

- Reports of shoulder, hand and Achilles tendon ruptures in patients on quinolones.
- Achilles tendon most common site.
- Can occur anytime during the course of treatment and even after treatment.
- Risk is greatest if corticosteroids are being used, and in older patients

# Quinolones and Arrythmias

- Retrospective review of large prescription drug plan database in Canada. Patients treated for respiratory coditions from 1990 to 2005 were included
- 605,127 patients met inclusion criteria, 1838 cases of serious arryhtmia, 4.7/10,000 person years
- In nonhospitalized patients had a RR 1.76 if on a fluoroquinolone. Risk highest in new users and with moxifloxacin (10.8/10,000) and ciprofloxacin( 5.4/10,000). Highest risk was with gatifloxacin (30/10,000)
- Clin Infect Dis 2012; 55:1457-1465

# FDA Fluoroquinolone Warning 12/2018

- Health care professionals should avoid prescribing fluoroquinolone antibiotics to patients who have an aortic aneurysm or are at risk for an aortic aneurysm (patients with PVD, hypertension, Marfan or Ehlers-Danlos syndrome and elderly patients(!))

# FDA Gabapentin Warning (12/2019)

- Respiratory depression with use of gabapentin/pregabalin in patients with respiratory risk factors defined as:
- Use of opioids/benzodiazepines/ antihistamines
- Patients with COPD
- 49 case reports submitted to FDA , with 12 deaths

- https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin

- 11) A 55 yo man has had diarrhea and foul smelling stool for the past 6 months. He has lost 15# during that time.He has a PMH of depression ,GERD, hyperlipidemia and hypertension. His meds include: sertraline, omeprazole, ezetimibe, rosuvastatin and olmesartan. What is the most likely cause of his symptoms?

A) Chronic pancreatitis
B) Sertraline
C) Omeprazole
D) Ezetimibe
E) Olmesartan

# Olmesartan and Sprue Like Enteropathy

- 22 patients seen at Mayo Clinic with sprue like symptoms while taking olmesartan over a 3 year period
- Celiac disease ruled out in all
- Most patients on 40mg of olmesartan. All had Villous atrophy (15) or submucosal collagen deposition
- All recovered when olmesartan was stopped
- Mayo Clin Proc. 2012 Aug;87(8):732-8.

# Drug Induced Hyponatremia

- Hydrochlorathiazide/indapamide (38%) (1)
- SSRI's (2,3)
- SNRI's (2,3)
- NSAIDs
- Carbemazipine (2)
- MDMA (ecstasy)

1)Saudi J Kidney Dis Transpl. 2013 Mar;24(2):281-5.

2) Int J Neuropsychopharmacol. 2012 Jul;15(6):739-48

3) Curr Drug Saf. 2013 Jul;8(3):175-80.

- 12) 85 yo woman is brought to the ED after a syncopal episode. Her care givers report a similar episode 2 weeks ago,but she recovered so quickly they did not seek evaluation for her.
- Meds: Omeprazole 20 mg, pravastatin 40 mg, citalopram 10 mg, albuterol, donepezil 10 mg, isosorbide mononitrate 60mg and calcium. On exam BP 100/60 P 55. ECG Bradycardia with normal intervals. What drug most likely caused of her syncope?

- A) Citalopram
- B) Pravastatin
- C) Donepezil
- D) Isosorbide
- E) Calcium

# Cholinesterase inhibitors and Syncope

- Cholinesterase inhibitors and bradycardia
  - ChE-I → RR bradycardia ↑ 1.4 (95% CI, 1.1–1.6)
  - Dose effect: donepezil > 10mg → 2.1 ↑ risk

J Am Geriatr Soc 2009;57:1997

- Clinical significance: ChE-I use associated with
  - Syncope: HR ↑ 1.76 (95% CI, 1.57-1.98)
  - ED visits for bradycardia: HR ↑ 1.69
  - Pacemaker placement: HR ↑ 1.49
  - Hip Fx: HR ↑ 1.18 (95% CI, 1.03-1.34)

Arch Intern Med 2009;169:867

# Citalopram and QT Prolongation

- Dose dependent QT prolongation
- Maximum dose recommended for citalopram 40 mg (maximum dose 20 mg for age >65)
- Escitalopram also can prolong QT, but less so. Other SSRI’s do not.
- Contraindicated in patients with congenital long QT syndrome
- Important interaction with CYP2C19 inhibitors (fluvoaxamine-luvox, fluoxetine, PPI’s, cimetidine, clopidogrel)
- Avoid use with other QT prolonging drugs

# Think Before Putting SSRI’S in the Drinking Water

- Probable increased risk of UGI bleed
- Often overlooked cause of hyponatremia
- Sexual dysfunction (20-50%)
- QT prolongation with citalopram

- 13) A 62 yo man with a hx of MI 4 years ago presents with right hip pain. He has had discomfort with walking for the past 6 months. Xray reveals moderate osteoarthritis. Most recent labs: Bun 6 Cr .8 Glu 100 What would be the most appropriate management plan?
- A) Acetaminophen
- B) Oxycodone
- C) Ibuprofen
- D) Diclofenac
- E) Celecoxib

# Risk of MI with NSAID Use

- Nationwide cohort study in Denmark. 99,187 patients with a mean age of 69
- Studied pharmacy records and medical records for all patients over age 30 with a first time admission for myocardial infarction between 1997 and 2009. Subsequent NSAID use was tracked
- HR for Death with NSAID use was 1.59 at 1year, 1.63 at 5 years. Risk for recurrent MI was 1.3 at 1 year, 1.41 at 5 years.
- Circulation 2012, 126: 1955-1963.

# NSAIDS and CHF in the elderly

- 365 cases of patients admitted with CHF compared to 658 control patients admitted without CHF
- NSAID users had an odds ratio of 2.1 for admission for CHF
- Odds ratio of 10.5 for first admit for CHF if patient had heart disease and used NSAIDS
- Risk of admission for CHF correlates with dose of NSAID and long acting drug

Arch intern med 2000;160:777-784

# NSAIDS and CHF

- Mechanism is interference with renal prostaglandin biosynthesis by inhibiting function of cyclooygenase (COX)
- NSAIDS also interfere with the effects of ACE inhibitors and diuretics

# What To Remember From This Talk

- Watch carefully for interactions with TMP/Sulfa , simvastatin and clarithromycin.
- Think twice before prescribing quinolones

# ANSWERS

1) D-Don’t worry
2) D- Ecstasy/escitalopram interaction
3) E- TMP/Sulfa
4) A- Acetaminophen
5) A- Prednisone
6) C- Levofloxacin
7) A- restart atorvastatin
8) D- Nifedipine-Clarithromycin interaction
9) D-Pramipexole
10) D- Stop levofloxacin
11) E- Olmesartan
12) C-Donepezil
13) A-Acetaminophen