Drug Interactions and Side Effects for 2023

What We Will Cover

- What medications have been in the news for toxicity and side effects in the last year?
- What are common drug interactions of which clinicians should be aware?
- Which common medications have frequent side effects and should be used less commonly?

- A 67 yo man presents for annual exam. PMH: Depression, GERD, and hypertension. He had an episode of major depression 6 years ago, and has been on citalopram ever since, with no recurrence of depressive symptoms- Medications: Citalopram, Famotidine, Valsartan and chlorthalidone. PE: BP 135/84 PHQ9 3
- What medication would be most reasonable to stop?
- A) Citalopram
- B) Famotidine
- C) Valsartan
- D) Chlorthalidone

Long-Term Antidepressant Use Tied to an Increase in CVD, Mortality Risk

- Cohort study of 222,000 primary care patients in large UK database
- ? If association with antidepressant use was linked to increased risk of mortality/heart disease
- SSRI treatment was associated with increased risks of CV (HR 1.34, 95% CI 1.02–1.77), CVD mortality (HR 1.87, 95% CI 1.38–2.53) and all-cause mortality (HR 1.73, 95% CI 1.48–2.03), and 'other' antidepressant treatment (Mirtazapine/ SNRI's) was associated with increased risk of CHD (HR 1.99, 95% CI 1.31–3.01), CVD (HR 1.86, 95% CI 1.10–3.15) and all-cause mortality (HR 2.20, 95% CI 1.71–2.84).

- *BJPsych Open, 2022 8*(5), E164.

Symptoms of SSRI Withdrawal Syndrome

- Paraesthesia
- Numbness
- Shock like sensations (“Brain Zaps”)
- Tremor
- Flu like symptoms
- Fatigue
- Headache
- Dizziness
- Insomnia
- GI symptoms: nausea,anorexia,vomiting,diarrhea)

Tapering Patients off SSRI's

- Usually do not need to taper patients off fluoxetine, unless on doses > 40 mg (long half life)
- Paroxetine is the biggest problem, taper ideally by 10 mg every 2-4 weeks
- Other SSRI's, taper no quicker than 4 weeks, longer tapers (up to 4 months) in patients who were on higher dose
- When in doubt, go slower!
- Lancet Psychiatry, The, 2019-06-01, Volume 6, Issue 6, Pages 538-546

- A 74 yo man with a hx of CAD presents to discuss ED. He would like to have effective therapy for his ED. He had an MI 4 years ago, stent placement, without subsequent problems. He has had a 10 year hx of angina with exertion, usually occurs predictably when walking uphill. Medications: Atorvastatin, Metoprolol, Aspirin, NTG (sl).
- BP 130/80 P66
- What would you recommend?
- A) Sildenafil
- B) Vacuum device
- C) Alprostadil
- D) Testosterone
- E) Penile implant

Is Nitroglycerine Deadly with Phosphodiesterase inhibitors?

- In a case crossover design, using nationwide Danish health registry over the period of 2000 to 2018. In 2000 the rate of coprescribing of phosphodiesterase inhibitors in ischemic heart disease patients on nitrates was .9 per 100 persons/yr and rose to 19.5 prescriptions per 100 persons/year in 2018. During this same time, no statistically significant association was found between the coprescription of nitrates with PDE5 inhibitors and the risk for MI, cardiac arrest, syncope, stroke or adverse drug event. (1)

- In a randomized, placebo controlled , crossover trial. Participants received sildenafil 100 mg or placebo, then received intravenous NTG. Patients who received sildenafil had a 4-6 mm systolic BP drop compared to placebo. There was no difference in severe events between the sildenafil and placebo groups. The blood levels of nitroglycerine in this study were very likely much higher than the levels that occur with SL NTG (2)
- 1) Ann Intern Med. 2022. PMID: 35436155
- 2) Crit Care Med 2007; 35:1863–1868.

Drug Interactions You Need To Be Aware Of

Drug-Drug Interactions In Community Older Adults- Meta-analysis

ACEI-K sparing diuretic (6 studies)

Amiodarone- Digoxin (5 studies)

Amiodarone- Warfarin (3 studies)

B Blocker- Verapamil (2 studies)

- Drugs Aging. 2023 Jan 24.

- A 47 yo man with sarcoidosis presents with multiple skin abscesses on his right arm. Drainage of the abscess gram stains for gram positive cocci in clusters. The patient is taking prednisone, methotrexate, pantoprazole and sertraline. What medication would be the most appropriate?
- A) TMP/Sulfa
- B) Doxycycline
- C) Linezolid
- D) Levofloxacin

Potential Drug Interactions

- Trimethoprim and Methotrexate
- Sertraline and Linezolid
- Levofloxacin and Prednisone

Trimethoprim- Methotrexate Interaction

- Coadministration of methotrexate with trimethoprim increases free methotrexate levels and reduces renal clearance for free methotrexate
- Multiple cases of pancytopenia and death have been reported in patients receiving lower dose methotrexate/standard dose TMP/Sulfa

- journal of Clinical Pharmacy and Therapeutics, 2013, 38, 203–205

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

Drug Interaction- Serotonin 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, trazodone)

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 Levothyroxine 100 mcg.

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

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) Famotidine
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.

Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid)

- Highlights of the do not use/hold list

Amiodarone

Clopidogrel

St John's Wort

Rivaroxaban

Simvastatin/lovastatin/rosuvastatin/atorvastatin

Phenytoin

Tamsulosin

Work arounds For Common Drugs When Taking Nirmatrelvir/Ritonavir

- Apixiban- can reduce dose to 2.5 mg BID if on 5mg, or could hold while on Nirmatrelvir/Ritonavir
- Fluconazole- if single dose, nothing needs to be done
- Atorvastatin Rosuvastatin- if patients absolutely can’t stop, can reduce dose by 50%

Medications That Are Scary

- 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

Donepezil Side Effects

- Diarrhea, nausea, and vomiting are common; prevalence increases with higher dosages
- May increase gastric acid secretion and increase the risk of gastrointestinal bleeding and stomach ulcers.
- May produce a slow heart rate (bradycardia) or heart block via an effect on the sinoatrial or AV nodes, even in people without any known cardiac conduction abnormalities.
- May cause weight loss at higher dosages
- May Cause urinary incontinence

NNT and NNH for Donepezil

- NNH 4-5 (rates as high as 25 % for Nausea with 10 mg dose)
- NNT 10-100 (10 for Cognitive function, up to 100 for global function)

- J Am Geriatr Soc. 2013 Jul;61(7):1170-4.

A 46-year-old woman with diabetes and seizure disorder presents with nausea and fatigue. Physical exam is unremarkable.Meds: Empagliflozin 25 mg daily, metformin 850 mg bid, phenytoin 300 mg daily, topiramate 400 mg daily, esomeprazole 40 mg daily Labs: Na^+ 133, K^+ 3.9, Cl^- 112, HCO_3^- 13, Glu 158, Bun 18, Cr 1.0

What is the most likely cause of this patient's acidosis?

A. Phenytoin
B. Topiramate
C. Metformin
D. Esomeprazole

Topiramate and Acidosis

- Topiramate acts as a carbonic anhydrase inhibitor
- Metabolic nonanion gap hyperchloremic acidosis can occur
- Average drop in bicarbonate is 4, but can be severe, especially in the setting of surgery
- Also raises serum uric acid levels

Side Effects of Topiramate

- Paresthesia
- Cognitive impairment
- Dizziness
- Drowsiness
- Decreased Sweating

A 85 yo man is brought to the ED for evaluation of weakness and nausea. He was diagnosed 10 days ago with prostatitis. His other problems include hypertension, CHF and CKD. Meds: Carvedilol, furosemide, TMP/Sulfa, verapamil, digoxin. Exam- BP 100/60 P-100 T 36.9 lower extremity edema present. Lab: Na- 132 K -6.8 BUN 37 Cr- 2.3. Two weeks ago, creatinine was 1.6 and K was 4.8. What is the most likely cause of his hyperkalemia?

A) CKD

B) Carvedilol

C) TMP/Sulfa

D) Verapamil

E) Digoxin

Trimethoprim-Sulfamethoxazole and Hyperkalemia

- Population based, nested case-control study of patients 66 or older who were receiving and ACEI or ARB (14 years)
- Case patients were those who had hyperkalemia within 14 days of receiving an antibiotic. For each case patient 4 controls were matched.
- 4148 admissions due to hyperkalemia. Compared to amoxicillin the relative risk for hyperkalemia with TMP-sulfa was 6.7 (CI 4.5-10) . No other antibiotic posed a significant risk for hyperkalemia.
- Arch Intern Med 2010; 170(12): 1045-1049.

TMP/Sulfa and Sudden Death

- **OBJECTIVE:** To determine whether the prescription of co-trimoxazole with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker is associated with sudden death.
- Of 39,879 sudden deaths, 1027 occurred within seven days of exposure to an antibiotic and were matched to 3733 controls.
- Relative to amoxicillin, co-trimoxazole was associated with an increased risk of sudden death (adjusted odds ratio 1.38, 95% confidence interval 1.09 to 1.76).
- BMJ. 2014 Oct 30;349

Trimethoprim Induced Hyperkalemia

- More common in elderly and patients with renal impairment
- More likely if patient is on an ACEI or ARB
- More likely if patient is receiving high doses of steroids
- Mechanism is that trimethoprim acts like amiloride, a potassium sparing diuretic, and reduces urinary potassium excretion by 40%

TMP/Sulfa Side Effects

- Skin rash- Some serious (Stevens-Johnson, Toxic epidermal necrolysis), rash in up to 50% of AIDS patients
- Hyperkalemia
- Hepatic dysfunction (often connected with skin rash)

When To Avoid TMP/Sulfa

- Elderly patients
- Patients on ACEI/ARBS/Spironolactone
- Patients on Warfarin
- Patients on Methotrexate

FDA Alert on Clarithromycin (2-2018)

- The U.S. Food and Drug Administration (FDA) is advising caution before prescribing the antibiotic clarithromycin (Biaxin) to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later.
- This was first noticed in the CLAIRCOR study in 2005 (FDA warning)

Biaxin of Evil?

- Severe drug interaction with colchicine (10% fatality rate with concominant therapy *)
- Severe drug interaction with statins
- Severe drug interaction with dihydropyridines
- Similar drug (Azithromycin) with minimal interactions available
- * Clin Infect Dis. 2005 Aug 1;41(3):291-300

What to Remember

- Sildenafil ok to use in patients with a SL NTG prescription
- Paxlovid can be used in patients on apixaban, using a lower dose of apixaban or holding the apixaban if clinically reasonable- other drug interactions can also be managed
- TMP/Sulfa has very important drug interactions with methotrexate, warfarin, and ACEI/ARBS/Spironolactone- should not be used unless under duress in the elderly

Questions ?

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