

Drug Interactions And Side Effects for 2025

Disclosure of Financial Relationships

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



- | A 45 yo woman presents with increasing tremor in her arms, and new tremor in her legs. These have been present for the past 3 weeks. She was in a MVC 6 weeks ago and sustained a neck injury as well as increased fear , anxiety and insomnia since the MVC. Exam shows a postural tremor which is mild. Current medications: Sertraline, zolpidem, tramadol, naproxen.
- | Which medication is the most likely cause of the tremors?
- | A) Sertraline
- | B) Zolpidem
- | C) Tramadol
- | D) Naproxen

SSRI's and Tremors

- | Has been described with all SSRI's
- | Tremor is usually postural
- | Tremor usually resolves after discontinuation, but in one series of fluoxetine induced tremor it persists for months*

| *Parkinsonism Relat Disord. 2002 Jun;8(5):325-7

| Prim Care Companion CNS Disord. 2003 Sep 14;25(5):23cr03496.

SSRI's and Risk of GI Bleeding

- | SSRI vs placebo OR 1.41 (CI 1.27-1.57), $p < .00001$ (1)
- | SSRI vs placebo OR 1.66 (1.44-1.92) (2)
NNH (low risk) 3177, NNH high risk 881
- | SSRI + NSAID OR 4.25 (2.82-6.42) (2)

1) Pharmacological Research 2017: 118: 19-32

2) [Am J Gastroenterol.](#) 2014 Jun;109(6):811-9.

SSRI's AND Hyponatremia

- | Older age
- | Female
- | Concomitant diuretic use
- | Low body weight

Risk of Hyponatremia with SSRI Combined With Other Drugs

- | SSRI alone 0.02% (Age over 65 0.07%)
- | SSRI + ACEI 0.27% (Age over 65 0.44%)
- | SSRI + diuretic 0.14% (Age over 65 0.23%)
- | SSRI+ ACEI+ diuretic 0.37%

Yawning as a Side Effect of SSRI's

- | Yawning has been reported as an SSRI side effect, with yawning occurring 40-150 times a day
- | Resolution of yawning when SSRI stopped
- | Somewhat dose dependent *

* Cureus. 2024 Jun 3;16(6):e61559.

International Journal of Neuropsychopharmacology, Volume 3, Issue 3, September 2000, Pages 275–276

- | 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.
- | Also, Even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent MI in patients with prior MI. (*Circulation*. 2011;123:2226-2235.)

CV Risk OF NSAID Treatment After

MI J Am Coll Cardio 2020;4:76(5).

NSAID	Hazard Ratio
NO NSAID	1.00
Any NSAID	6.96
Naproxen	10.60
Ibuprofen	8.17
Diclofenac	7.27

GI Bleeding Risk AND NSAIDS in Patients Post MI

J Am Coll Cardio 2020;4:76(5).

NSAID	Hazard Ratio
No NSAID	1.00
Naproxen	7.71
Ibuprofen	4.44
Diclofenac	5.05
Celecoxib	4.32

NSAIDS and New Onset CHF

- | Using nationwide Danish registers, patients diagnosed with T2DM from 1998 to 2021 and without previous HF, rheumatic disease, or use of NSAIDs 120 days before diagnosis of CHF. Associations between NSAIDs and first-time HF hospitalization were investigated using a case-crossover design with 28-day exposure windows
- | 331,189 patients with T2DM: 23,308 patients were hospitalized with HF during follow-up, and 16% of patients claimed at least 1 NSAID prescription within 1 year. Short-term use of NSAIDs was associated with increased risk of HF hospitalization (OR: 1.43; 95% CI: 1.27-1.63), especially in patients >80 (OR: 1.78; 95% CI: 1.39-2.28)
- | JACC VOL. 81, NO. 15, 2023:1459-70.

FDA Warning About NSAIDS and CV Risk

- | FDA strengthened NSAID cardiovascular risk warning 7/2015

- | Question 4: 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

Question 6: 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.

Common Drugs with Side Effects

Semaglutide and NAION

- | Danish study of 424,152 Danish patients with Type 2 DM (all Danish pts with type 2 DM)
- | During 1,915,120 person-years of observation, 218 persons developed Nonarteritic anterior ischemic optic neuropathy (NAION). Semaglutide exposure was associated with a higher incidence rate (0.228 vs. 0.093 per 1000 person-years, $p < 0.001$) and predicted a higher risk of upcoming NAION (HR 2.19, 95% confidence interval 1.54 - 3.12)
- | 1/4000 vs 1/10,000
- | Int J Retina Vitreous. 2024 Dec 18;10(1):97.

I A 71 yo man with type 2 DM and recent hospitalization for ACS presents for follow up. He had a stent placed with resolution of his chest pain. He has been doing very well, but has been having dyspnea since hospitalization. Medications: Lisinopril, aspirin, ticagrelor, empagliflozin, metformin, and rosuvastatin.

PE: BP 120/80 P 80 O2 sat 97%. Chest – clear cardiac- no murmurs. LE- no edema

Labs: HB 14 HCT 42 BNP 45 Chest Xray- unremarkable

Most likely etiology of dyspnea?

- A) Pulmonary embolus
- B) Lisinopril
- C) Ticagrelor
- D) Aspirin
- E) Empagliflozin

Ticagrelor and Dyspnea

STUDY	% Dyspnea Ticagrelor	% Dyspnea Clopidogrel
OFFSET/ONSET	38.6	9.3
RESPOND	13	4
DISPERSE-1	10	0
DISPERSE-2	15.8	6.4

Drug Interactions With Paxlovid (Nirmatrelvir/Ritonavir)

| Highlights of the do not use/hold list

Amiodarone

Clopidogrel

St John's Wort

Rivaroxaban

Simvastatin/lovastatin/rosuvastatin/atorvastatin

Phenytoin

Tamsulosin

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.

Angiotensin Receptor Blocker-Related Sprue-like Enteropathy

- | All reports of ARB-related SE from January 2017 to December 2021 were downloaded from the FAERS database.
- | Sprue-like enteropathy was identified in 4337 cases (4.1% of total reports). Of these, 4240 cases (98.0%) of ARB-related SE were reported in patients using products with olmesartan, and 97 cases of SE were reported for all other ARBs (eprosartan, losartan, telmisartan, irbesartan, valsartan, and candesartan).
- | Ann Pharmacother 2024 May;58(5):494-500.

ARB's and Celiac disease

- | 1849 patients with celiac disease, including 1460 women and 389 men, with a median age of nearly 50 years at diagnosis. 120 started an ARB before celiac disease diagnosis and 142 started one after diagnosis.
- | Taking an ARB was associated with increased hazard ratios [HRs] for low hemoglobin, iron deficiency, diarrhea, and abdominal pain.
- | For those starting an ARB after diagnosis, problems with low hemoglobin (HR, 1.98) and iron deficiency (HR, 1.72) occurred.
- | Hujoel I and Hujoel M, abstract American College of Gastroenterology (ACG) 2024 Annual Scientific Meeting.

- | A 67 yo woman presents to clinic with concerns about diplopia. She has had intermittent vertical diplopia over the past 3 months. She has a history of hypertension, depression , hypothyroidism and chronic neck pain. Current medications include: Amlodipine, Fish oil, fluoxetine, pregabalin, levothyroxine. Exam is unremarkable , including normal eye movements.
- | Which medication that she is taking is associated with diplopia?
 - A) Amlodipine
 - B) Fish oil
 - C) Fluoxetine
 - D) Pregabalin
 - E) Levothyroxine

Diplopia and Antiepileptic Drugs

- | Oxcarbazepine OR 7.996
- | Levetiracetam OR 7.472
- | Lamotrigine OR 5.258
- | Pregabalin OR 3.048
- | Topiramate OR 2.660
- | Gabapentin OR 1.966

J Huazhong Univ Sci Technolog Med Sci 2012 Aug;32(4):557-562.

| 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, gabapentin, 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) Gabapentin

| E) Escitalopram

Drug Induced Edema

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

Gabapentin and Fall Risk

- | Retrospective case-control study of 1,813 patients aged 65-89 on chronic opioid therapy (2017-2020), excluding those with a fall history, analysis focused on the first fall occurrence.
- | Out of eligible patients, 122 (6.73%) experienced falls during opioid therapy, with 232 (12.80%) having concurrent gabapentin use. Concurrent use significantly increased fall risk (AOR = 1.73; 95% CI: 1.08-2.78).
- | J Pain Palliat Care Pharmacother. 2024 Jun 10:1-7.

Gabapentin and Hip fracture

- | Case-case-time-control study in patients hospitalized for hip fracture in Victoria, Australia, between March 1, 2013, and June 30, 2018, with at least 1 prescription for a gabapentinoid before fracture.
- | Gabapentinoid dispensing was associated with increased odds of hip fractures (OR, 1.96; 95% CI, 1.66-2.32).
- | The association between gabapentinoid dispensing and hip fracture was higher in patients with high frailty scores (OR, 1.75; 95% CI, 1.31-2.33) and CKD (OR, 2.41; 95% CI, 1.65-3.52).
- | JAMA Netw Open. 2024 Nov 4;7(11):e2444488.

Gabapentinoids and Risk for Severe Exacerbation in Chronic Obstructive Pulmonary Disease

- | Time-conditional propensity score–matched, new-user cohort study.
- | The cohort included 356 gabapentinoid users with epilepsy, 9411 with neuropathic pain, and 3737 with other chronic pain, matched 1:1 to nonusers. Compared with nonuse, gabapentinoid use was associated with increased risk for severe COPD exacerbation HR, 1.39 [CI, 1.29 to 1.50].
- | Ann Intern Med. 2024 Jan 16

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>



| A 66 yo woman is discharged from the hospital after an MI. Her discharge medications include atorvastatin 40 mg, lisinopril 20 mg, ASA 81 mg and clopidogrel 75mg. At her follow up appt she mentions that she has muscle pain and stiffness in both legs and her back. Labs: TSH 2.0 Vitamin D 40 . She stops the atorvastatin for 2 weeks with resolution of her symptoms

| What do you recommend?

| A) Restart atorvastatin

| B) Start Simvastatin

| C) Start Rosuvastatin twice a week

| D) Start Ezetimibe

| E) Start a PCSK9 inhibitor

SAMS- How Good is Rechallenge?

- | Retrospective study of 118 patients referred to a lipid clinic as being statin intolerant (muscle symptoms on 2 or more statins)
- | Patients were either rechallenged with the same statin, a different statin or non statin therapy
- | Tolerability 71% same statin, 53% statin switch and 57% non statin therapy
- | Can J Card 2017;33:666-673

Nocebo Effect and SAMS

- | 60 patients with a hx of SAMS were entered into the trial
- | The patients received four bottles containing atorvastatin at a dose of 20 mg, four bottles containing placebo, and four empty bottles; each bottle was to be used for a 1-month period according to a random sequence.
- | The mean symptom intensity was 8.0 during no-tablet months (95% CI, 4.7 to 11.3), 15.4 during placebo months (95% CI, 12.1 to 18.7; $P < 0.001$ for the comparison with no-tablet months), and 16.3 during statin months (95% CI, 13.0 to 19.6; $P < 0.001$ for the comparison with no-tablet months and $P = 0.39$ for the comparison with placebo months) .
- | N Engl J Med 2020; 383;22

Statin Associated Muscle Symptoms

- | 120 patients with prior SAMS enrolled in 8 week ,cross over, placebo controlled trial simvastatin 20 mg or placebo. Vitamin d levels measured during each phase
- | 43 (35.8%) experienced muscle pain on simvastatin and not placebo (True SAMS). 21 (17.5%) had no pain on either treatment, 21 (17.5%) had pain with both treatments, and 35 (29%) had pain only with placebo.
- | Patients with true SAMS had a higher CK
- | Baseline and on statin CK was inversely correlated with vitamin D level
- | Atherosclerosis 2017; 256: 100-104

SAMS Large N-1 Trial

- | Design: A series of 200 double-blinded N-of-1 trials
- | Participants: Patients who were considering discontinuing statin use and those who had discontinued statin use in the last 3 years because of perceived muscle symptoms.
- | Interventions: Participants were randomised to a sequence of six 2-month treatment periods during which they received 20 mg of atorvastatin daily or a matched placebo
- | Results: Among people who previously reported severe muscle symptoms while taking statins, this series of randomised N-of-1 trials found no overall effect of statins on muscle symptoms compared with the placebo
- | Health Technol Assess 2021;25(16)

Approach to Management of Myalgias on Statins

- | Check CK ,TSH, Vitamin D
- | Review for drug interactions- especially ca channel bl
- | Stop statin, when symptoms disappear restart statin at lower dose (up to 70% success with same statin rechallenge*) or change statin (30-40% success*)
- | Can switch to intermittent potent statin
- | Ezetimibe or PCSK9 inhibitor in appropriate patients

| A 64 yo woman presents for routine follow up. Her medical problems are depression, GERD, hyperlipidemia and asthma. Medications: Fluoxetine, Bupropion, Lansoprazole, Pravastatin, albuterol and montelukast. Her exam is unremarkable. Labs show a Cr of 2.3 (baseline 1.1 , 3 years ago). What medication is most concerning for association with CKD?

- | A) Fluoxetine
- | B) Bupropion
- | C) Lansoprazole
- | D) Pravastatin
- | E) Montelukast

PPI's and CKD

- | 12 year follow up of cohort with initial baseline GFR >60. A replication cohort study was done of a different group.
- | 10,482 individuals were studied in the initial cohort, 248, 751 in the replication trial.
- | Self reported PPI use in the original trial or PPI prescription in replication trial were used to measure PPI exposure
- | In the 1st cohort, adjusted HR 1.50; 95%CI, 1.14-1.96 for PPI users, in replication trial, adjusted HR, 1.24; 95%CI, 1.20-1.28. Twice daily dosing posed a higher risk , (HR 1.46 vs 1.15)
- | JAMA Internal Medicine 2016; 176 (2):238-246.

PPI's and AKI

- | Population based cohort study
- | The primary outcome was hospital admission with acute kidney injury within 120 days
- | 290, 592 individuals who commenced PPI therapy and an equal number of matched controls. The rates of acute kidney injury (13.49 v. 5.46 per 1000 person-years, respectively; hazard ratio [HR] 2.52, 95% CI 2.27 to 2.79) and acute interstitial nephritis (0.32 vs. 0.11 per 1000 person-years; HR 3.00, 95% CI 1.47 to 6.14) were higher among patients given PPIs than among controls.
- | [CMAJ Open.](#) 2015 Apr 2;3(2):E166-71.

- | A 48 yo woman presents for evaluation for possible depression. She has had several episodes of major depression in her life, and feels like she has another episode. She has a hypertension, hyperlipidemia, type 2 DM and GERD. Medications: Telmisartan, amlodipine, rosuvastatin, empagliflozin, semaglutide and omeprazole. Her PHQ9 is 12
- | Which drug that she is currently taking has the greatest association with depression?
- | A) Telmisartan
- | B) Amlodipine
- | C) Rosuvastatin
- | D) Empagliflozin
- | E) Omeprazole

Use of proton-pump inhibitors is associated with depression: a population-based study

- | Mood was assessed by the 30-item Geriatric Depression Scale (GDS) in all 344 inhabitants of Tuscania (Italy) aged 75 years and over, without exclusion criteria; depression was defined by a GDS score ≥ 11 .
- | Use of PPIs was associated with a higher GDS score in linear regression analysis (B = 2.43; p = 0.014)
- | Higher PPIs dosages were associated with increased probability of depression (p for trend = 0.014)
- | International Psychogeriatrics , Volume 30 , Issue 1 , January 2018 , pp. 153 - 159

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
- | Increased risk of C. difficile, and recurrent C Diff and more severe C diff. FDA warning 2/12
- | CKD/ AKI
- | Depression?

