Did You Know?

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Clinically Significant Drug Interactions

- A study published in JAMA Internal Medicine in 2016, found 36% of older adults regularly use 5 or more medications or supplements and 15% were at risk for potential major drug interactions.[1]
- Drug interactions can result in adverse effects that can lead to prolonged symptoms, disability, and even death.
- Types of drug interactions:
  - **Pharmacodynamic**: occurs when 2 medications given concurrently, act at the same receptor site. This can lead to an additive effect or a decreased effect depending on the medications.
  - **Pharmacokinetic**: occurs when one medication affects another medication's absorption, distribution, metabolism, or excretion.
- Several drug interactions are related to timing of administration. Please see December 2017 DYK: Medication Administration Drug Interactions for more information regarding interactions resulting from timing of administration of medications.
- Several drugs, when used concurrently, can increase the risk of QT prolongation. See August 2018 DYK for more information on medications that can prolong the QT interval.
- The following table includes several very important clinically significant drug interactions to be aware of (Note: table is not all-inclusive):

Drug One	Drug Two	Potential Adverse Outcome
TMP/SMX (Bactrim)	ACE inhibitor (i.e. lisinopril, benazepril, ramipril, etc.) OR ARBS (i.e. losartan, valsartan, etc.) OR Spironolactone (Aldactone)	Increased risk of hyperkalemia, especially in the presence of renal impairment.[2] Closely follow Potassium level if concurrent therapy is indicated.
TMP/SMX (Bactrim)	Warfarin (Coumadin)	Increased risk of bleeding. Monitor INR closely if concurrent therapy is indicated.
Antibiotics	Warfarin (Coumadin)	Almost all antibiotics can increase the risk of bleed when used with Warfarin due to the antibiotics ability to decrease intestinal flora/bacteria that produce Vitamin K. Antibiotics such as the fluoroquinolones, macrolides, and sulfonamides, also inhibit warfarin's metabolism, increasing its concentration and anticoagulation effects, putting the patient at an increased risk of bleed. Some suggest monitoring of INR every other day during antibiotic therapy if concurrent use is deemed necessary. [3]

Drug One	Drug Two	Potential Adverse Outcome
TMP/SMX (Bactrim)	Phenytoin (Dilantin)	Increased risk of Phenytoin toxicity. The 2019 AGS Beers Criteria recently added this interaction as a combination that should be avoided. Consider close monitoring of Phenytoin serum concentrations and monitoring for s/s of phenytoin toxicity if concurrent therapy is necessary.
TMP/SMX, Clarithromycin, Levofloxacin, Ciprofloxacin, Metronidazole	Glyburide or Glipizide	Increased risk of hypoglycemia. [4]
Potassium Chloride tablets (K-Dur)	Anticholinergic Drugs (i.e. antihistamines, antimuscarinics, tricyclic antidepressants, etc.)	Anticholinergic drugs decrease GI motility, making it more likely for Potassium Chloride tablets to adhere to the GI mucosa, causing ulceration. Consider liquid Potassium or powder in those patients on concurrent anticholinergic medications.
Clarithromycin or Erythromycin	Calcium Channel Blockers (Diltiazem, Verapamil, Amlodipine, etc.)	Coadministration has been associated with an increased risk of hypotension and shock. Azithromycin may be preferred if the use of a macrolide antibiotic is necessary.
Clarithromycin or Erythromycin	Atorvastatin, Simvastatin, Lovastatin	Adding the antibiotics to the statins listed, has been shown to increase the risk of rhabdomyolysis more than 2-fold in older adults.[5]
Clarithromycin	Digoxin	Clarithromycin has been reported to increase the digoxin AUC by 70% when digoxin is administered orally. This puts the patient at an increased risk of Digoxin Toxicity. Measure serum digoxin concentrations before initiating clarithromycin. Reduce digoxin concentrations by decreasing the oral digoxin dose by approximately 30 to 50% or by modifying the dosing frequency and continue monitoring. (Clinical Pharmacology)
Digoxin	Amiodarone	Amiodarone increases orally administered digoxin serum concentration by 70% when given concomitantly. Measure serum digoxin concentrations before initiating amiodarone. According to the manufacturer of amiodarone, the digoxin dose should be reduced by 50% upon initiation of amiodarone. The manufacturer of digoxin recommends measuring the serum digoxin concentration before initiating amiodarone and reducing the serum digoxin concentration by reducing the oral dose by approximately 30 to 50%. (Clinical Pharmacology)
NSAIDS (ibuprofen, naproxen) or Aspirin	Antiplatelets, Anticoagulants (Plavix, Warfarin, Xarelto, Eliquis, Pradaxa)	Increased risk of bleeding. Monitor closely for signs/symptoms of bleeding if concurrent therapy is indicated and utilize NSAID for shortest duration necessary.

Drug One	Drug Two	Potential Adverse Outcome
NSAIDs, Aspirin, Antiplatelets, Anticoagulants	SSRIs (Zoloft, Celexa, Lexapro, Paxil, Prozac, etc.)	Increased risk of bleeding.
Loop diuretics (i.e. Furosemide) or ACE inhibitor (i.e. lisinopril, etc)	Lithium	Increased risk of Lithium toxicity. If concurrent use is deemed necessary, monitor lithium concentration closely.
Simvastatin (Zocor)	Amiodarone Dronedarone (Multaq) Amlodipine (Norvasc) Verapamil/Diltiazem Gemfibrozil	Increased risk of myopathy when Simvastatin used with listed medications. Maximum daily doses of simvastatin listed below if used concurrently: Simvastatin/Amiodarone-max dose of 20 mg/day Simvastatin/Dronedarone-max dose of 10 mg/day Simvastatin/Amlodipine—max dose of 20 mg/day Simvastatin/Verapamil or Diltiazem-max dose of 10 mg Gemfibrozil—use is contraindicated with simvastatin
Lovastatin (Mevacor)	Amiodarone Dronedarone (Multaq) Verapamil/Diltiazem (Cardizem)	Increased risk of myopathy when Lovastatin is used concurrently with listed medications. A reduced dose of Lovastatin is recommended per below: Lovastatin/Amiodarone-max dose of 40 mg/day Lovastatin/Multaq-max dose of 20 mg per FDA (guidelines recommend 10 mg) Lovastatin/Diltiazem-max dose of 20 mg/day
Atorvastatin (Lipitor)	Diltiazem (Cardizem) or Verapamil (Calan)	Coadministration of atorvastatin 40 mg with diltiazem 240 mg was associated with a higher plasma concentration of atorvastatin. Increased concentrations of atorvastatin are associated with an increased risk of myopathy and rhabdomyolysis. Consider using Pravastatin (Pravachol) or Rosuvastatin (Crestor) instead of Lipitor. (Per CP)

References:

1. JAMA Intern Med. 2016;176(4):473-482. doi:10.1001/jamainternmed.2015.8581
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4. Parekh TM, Raji M, Lin YL, et al. Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas. JAMA Intern Med 2014; 174:1605-12.
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6. Clinical Pharmacology. https://www.clinicalkey.com/pharmacology. Accessed 7/23/19.