Institute for Safe Medication Practices Canada
Institut pour l'utilisation sécuritaire des médicaments du Canada

Drug-Drug Interactions in the Geriatric Population – Summary of Selected Pharmacoepidemiological Studies in Ontario (Nested Case-Control, Retrospective Cohort, and Case Cross-Over Studies)*

Drug-Interaction Pair		Demographics / Background Information	Comments
Continuous Medication	**Added Medication**		
Glyburide[1]	Trimethoprim-sulfamethoxazole (TMP-SMX)	**Study Population:** Older than 66 years treated with glyburide. A total of 909 cases. **Drug Toxicity/ Adverse Event:** Hypoglycemia **Possible Mechanism of Action:** Sulfamethoxazole can directly cause pancreatic insulin release (at higher doses due to structural similarity to sulfonylurea) in patients with renal impairment. Sulfonamide antibiotics inhibit CYP 2C9. Glyburide is metabolized by CYP 2C9.	The concomitant use of TMP-SMX with glyburide was associated with increased risk of hospitalization due to hypoglycemia in the elderly. Juurlink et al. estimated that patients who were hospitalized due to hypoglycemia while using glyburide were around 6 times more likely to have been treated with TMP-SMX within 1 week.
Digoxin[1]	Clarithromycin	**Study Population:** Older than 66 years treated with digoxin. A total of 1,051 cases. A total of 51,896 controls. **Drug Toxicity/ Adverse Event:** Digoxin toxicity **Possible Mechanism of Action:** Clarithromycin inhibits P-glycoprotein which leads to decreased renal clearance of digoxin.	The concomitant use of clarithromycin and digoxin was associated with increased risk of hospitalization due to digoxin toxicity in the elderly. Juurlink et al. estimated that patients who were hospitalized due to digoxin toxicities while using digoxin were around 12 times more likely to have been treated with clarithromycin.
Angiotensin-converting enzyme inhibitors	Potassium-sparing diuretics (amiloride, triamterene, or	**Study Population:** Older than 66 years treated with an ACEI. A total of 523 cases. A total of 25,807	The concomitant use of ACEIs and potassium sparring diuretics was associated with an increased risk of hospitalization

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(ACEIs)[1]	spironolactone)	controls. **Drug Toxicity/ Adverse Event:** Hyperkalemia **Possible Mechanism of Action:** ACEIs and potassium sparing diuretics both increase serum potassium levels. When used together they may precipitate hyperkalemia.	due to hyperkalemia in the elderly. Juurlink et al. estimated that patients who were hospitalized due to hyperkalemia while using ACEIs are 20 times more likely to have been treated by potassium sparing diuretics.
Lithium[2]	ACEIs or loop diuretics	**Study Population:** Older than 66 years treated with lithium. A total of 413 cases and 1,651 controls. **Drug Toxicity/ Adverse Event:** Lithium toxicity **Possible Mechanism of Action:** ACEIs reduce glomerular perfusion via inhibition of angiotensin II.	Concomitant use of lithium and ACEIs or loop diuretics was associated with increased risk of hospitalization due to lithium toxicities in the elderly. Juurlink et al. estimated that patients who were hospitalized due to lithium toxicity while using lithium are 2 times more likely to have been treated by ACEIs or loop diuretics.
Warfarin[3]	Nonsteroidal anti-inflammatory drugs (NSAIDs) [nonselective NSAIDs or COX-2 inhibitors (celecoxib and rofecoxib)]	**Study Population:** Older than 66 years treated with warfarin. A total of 361 cases. A total of 1,437 controls **Drug Toxicity/ Adverse Event:** Upper gastrointestinal (GI) hemorrhage **Possible Mechanism of Action:** S-warfarin (active enantiomer) and NSAIDs are substrates for CYP 2C9. Both NSAIDs and warfarin can increase risk of GI bleeding.	Concomitant use of warfarin and NSAID or COX-2 inhibitor was associated with increased risk of upper GI hemorrhage in the elderly. Battistella et al. estimated that patients who were hospitalized due to an upper GI bleed while using warfarin were around 2 times more likely to have used an NSAID or COX-2 inhibitor within 90 days.
Digoxin[4]	Macrolide antibiotics	**Study Population:** Over the age of 66 treated with digoxin. A total of 1,659 cases. A total of 6,439 control cases. **Drug Toxicity/ Adverse Event:**	Concomitant use of digoxin and macrolide antibiotics may lead to increased risk of hospitalization in the elderly. Gomes et al. estimated that

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		Digoxin toxicity **Possible Mechanism of Action:** Macrolide antibiotics can reduce re-circulation of digoxin by reducing *Eubacterium lentum* in the gut. Clarithromycin may inhibit P-glycoprotein-mediated tubular secretion of digoxin.	patients who are hospitalized due to digoxin toxicity are 15 times more likely to be taking clarithromycin and 4 times more likely to be taking azithromycin or erythromycin.
Clopidogrel[5]	Proton pump inhibitors (PPIs)	**Study Population:** Over the age of 66 years treated with clopidogrel. A total of 734 cases. A total of 2,057 controls. **Drug Toxicity/ Adverse Event:** Re-infarction **Possible Mechanism of Action:** Clopidogrel is a pro-drug requiring activation by CYP 2C19. Omeprazole, lansoprazole and rabeprazole inhibit CYP 2C19 which leads to reduced anti-platelet action.	Concomitant use of clopidogrel and PPIs (except pantoprazole) is associated with increased risk of re-infarction in the elderly. Juurlink et al. report in patients who are hospitalized for a re-infarct and using clopidogrel are more likely to be using a PPI within 30 days. Pantoprazole was not associated with increased hospitalization.
ACEIs/ Angiotensin receptor blockers (ARBs)[6]	TMP-SMX	**Study Population:** Over the age of 66 years treated with ACEI or ARBs. A total of 369 cases. A total of 1,417 controls. **Drug Toxicity/ Adverse Event:** Hyperkalemia **Possible Mechanism of Action:** ACEIs and ARBs impair urinary potassium excretion TMP reduces urinary potassium excretion.	Concomitant use of TMP-SMX and ACEIs or ARBs is associated with increased risk of hospitalization due to hyperkalemia in the elderly. Antoniou et al. estimated in patients who are hospitalized for hyperkalemia and using ACEIs or ARBs are about 7 times more likely to have received TMP-SMX.
Warfarin[7]	TMP-SMX, ciprofloxacin	**Study Population:** Over the age of 66 years	Concomitant use of TMP-SMX or ciprofloxacin with warfarin

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		treated with warfarin. A total of 2,151 cases. A total of 10,201 controls. **Drug Toxicity/ Adverse Event:** Hemorrhagic complications **Possible Mechanism of Action:** TMP-SMX inhibits CYP 2C9. S-warfarin (active enantiomer) metabolized predominantly by CYP 2C9.	increases the risk of hospitalization due to hemorrhagic complications Fischer et al. estimated patients, who were hospitalized with hemorrhagic complications while using warfarin, are 3 times more likely to have been exposed to TMP-SMX and 2 times more likely to have been using ciprofloxacin
Tamoxifen[8]	Paroxetine	**Study Population:** 2,430 women over the age of 66 years treated with tamoxifen for breast cancer on concurrent treatment with a single selective serotonin reuptake inhibitor (SSRI). **Drug Toxicity/ Adverse Event:** Breast cancer mortality **Possible Mechanism of Action:** Tamoxifen is a pro-drug metabolized by CYP 2D6 to the active endoxifen. Paroxetine is a potent CYP 2D6 inhibitor and may reduce the activation of tamoxifen.	Kelly et al. report paroxetine use during tamoxifen treatment increases breast cancer mortality. The median overlap time of tamoxifen and paroxetine treatment in this study was 41%. It is estimated that this level of overlap would result in one additional breast cancer death at 5 years for every 20 women treated. This is a retrospective cohort study.
Calcium channel blockers (CCBs) (verapamil, diltiazem, nifedipine, amlodipine, or felodipine)[9]	Macrolide antibiotics (erythromycin, clarithromycin, and azithromycin)	**Study Population:** Over the age of 66 years treated with CCBs. A total of 7100 in cohort. A total of 176 cases. **Drug Toxicity/ Adverse Event:** Hypotension **Possible Mechanism of Action:** Two macrolides, erythromycin and clarithromycin, inhibit CYP 3A4. Azithromycin does not inhibit CYP 3A4. Calcium	Concomitant use of CCBs and macrolide antibiotics are associated with increased risk of hospitalization due to hypotension. Wright et al. found in patients who are admitted to hospital due to hypotension while using a CCB are more likely to have received clarithromycin or erythromycin prior to hospitalization. Azithromycin was not associated with

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		channel blockers are CYP 3A4 substrates.	hypotension. This is a case cross-over study.
Theophylline[10]	Ciprofloxacin	**Study Population:** Over the age of 66 treated with theophylline. A total of 180 cases. A total of 9,000 controls. **Drug Toxicity/ Adverse Event:** Theophylline toxicity **Possible Mechanism of Action:** Theophylline is metabolized by CYP 1A2. Ciprofloxacin is a potent inhibitor of CYP 1A2. Ciprofloxacin is a commonly used antibiotic given to chronic obstructive pulmonary disease (COPD) patients.	Concomitant use of theophylline and ciprofloxacin may lead to increased risk of hospitalization due to theophylline toxicity. Antoniou et al. estimated that patients hospitalized due to theophylline toxicity were 2 times more likely to have been treated with ciprofloxacin.
Phenytoin[11]	TMP-SMX	**Study Population:** Over the age of 66 years treated with phenytoin. A total of 796 cases. A total of 3,148 controls. **Drug Toxicity/ Adverse Event:** Phenytoin toxicity **Possible Mechanism of Action:** Phenytoin is metabolized by CYP 2C8. TMP-SMX is a potent CYP 2C8 inhibitor and may lead to increase in phenytoin level.	Concomitant use of phenytoin and TMP-SMX increases the risk of hospitalization due to phenytoin toxicity. Antoniou et al. estimated patients who are hospitalized due to phenytoin toxicity are 2 times more likely to have received TMP-SMX within 30 days.
Spironolactone[12]	TMP-SMX, Nitrofurantoin	**Study Population:** Over the age of 66 years treated with spironolactone. A total of 248 cases (median age, 82 years). A total of 783 controls (median age, 81 years). **Drug Toxicity/ Adverse Event:** Hyperkalemia	Concomitant use of TMP-SMX or nitrofurantoin with spironolactone has been associated with increased risk of hospitalization due to hyperkalemia. Antoniou et al. estimated that patients hospitalized due to hyperkalemia while using spironolactone are 12 times

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		Possible Mechanism of Action: Spironolactone and TMP-SMX both decrease urinary excretion of potassium.	more likely to have been using TMP-SMX and 2 times more likely to have been using nitrofurantoin.

*The information in this chart was taken from the individual drug interaction studies and does not necessarily represent the opinion of ISMP Canada. Healthcare organizations are encouraged to critically appraise these studies to determine the applicability to their specific practice settings.

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