

Integrating a Novel Medication Risk Score and Use of an Advanced Clinical Decision Support System into a Pharmacist- and Nurse-Coordinated Transition of Care Program to Mitigate Drug Interactions

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Article Type: Case Report

Compiled date: January 28, 2021

Volume: 2

Issue: 1

Journal Name: Clinical Case Reports Journal

Journal Short Name: Clin Case Rep J

Publisher: Infact Publications LLC

Article ID: INF1000079

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Keywords: Medication safety; Drug interaction; Transition of care; Pharmacist



Cite this article: Tranchina K, Turgeon J, Bingham J. Integrating a novel medication risk score and use of an advanced clinical decision support system into a pharmacist- and nurse-coordinated transition of care program to mitigate drug interactions. Clin Case Rep J. 2021;2(1):1–5.

Abstract

Purpose: Patients affected by polypharmacy are at higher risk for significant multi-drug interactions. Inadequate management of these multi-drug interactions in patients discharged from the hospital can lead to readmission and/or medication-related morbidity.

Case: The pharmacist identified drug interactions associated with the cytochrome P450 enzymatic system and P-glycoprotein during a medication safety review for an 86-year-old male. Clinical recommendations were made to mitigate these interactions and align the therapeutic regimen with national consensus guidelines based on patient characteristics. Overall, the pharmacist recommended that the provider deprescribe medications found to be unsafe in the elderly to improve the medication risk score associated with medication-related morbidity.

Conclusion: The interventions recommended by the pharmacist's interventions decreased the risk of adverse events and may have helped avoid hospital readmission. The case report lends evidence to support a clinical decision support system's role and its value towards improving patient health outcomes post-hospital discharge.

Introduction

Adverse Drug Events (ADEs) become more common as patients age, and the occurrence doubles for those that are 65 years and older [1]. However, many of these can be mitigated by identifying potential Drug-Drug Interactions (DDIs) [2]. The following case presentation describes a situation in which interventions proposed by a pharmacist during a medication safety review using an advanced clinical decision support system may have significantly improved patient outcomes. These comprise a decrease in the risk of ADEs and hospital readmission through DDI mitigation.

Case Presentation

Patient History: An 86-year-old male with a history of arthritis, asthma, Atrial Fibrillation (AFib), Coronary Artery Disease (CAD), insomnia, Type 2 Diabetes Mellitus (T2DM), Hyperlipidemia (HLD), Hypertension (HTN), and Benign Prostate Hypertrophy (BPH) was readmitted to the hospital cardiac unit after a recent discharge for pneumonia and AFib with rapid ventricular response rate. Upon admission, he complained of coughing that had not resolved since the previous admission nine days prior.

Differential Diagnosis and Treatment: An electrocardiogram showed a left bundle branch block, and the patient’s troponins were elevated with a peak of 1.7 ng/mL. He was also found to have an ejection fraction of 50%. Considering these discoveries, the patient was admitted for Non-ST Segment Elevation Myocardial Infarction (NSTEMI). The creatinine clearance was not decompensated while in the hospital. A percutaneous coronary intervention was performed required two drug-eluting stents. He was also diagnosed with heart failure with preserved ejection fraction (HFpEF). He was treated with diltiazem in the hospital for ventricular rate control,

then prescribed triple anticoagulation therapy for one month, and referred to a pharmacist- and nurse- coordinated transition of care program for discharge consultation services. The service included comprehensive medication management services one week and three weeks post-discharge. The pharmacist assessed for DDIs, drug-disease interactions, therapeutic duplications, ADEs, dosing concerns, high-risk medications in the elderly, medication adherence, cost-related barriers, and disease counseling services. See (Table 1) for the list of medications upon discharge prior to the pharmacist’s consultation.

Table 1: Medication List and Summary of Affinity and CYP450 Metabolic Pathways Pre-Pharmacist Consultation.

Drug	Dose	Frequency	Indication	1A2	2C9	2D6	3A4
Aspirin	81 mg	1 by mouth every evening	Stroke prevention	Non CYP			
Prasugrel	10 mg	1 by mouth daily	Stroke prevention				60%*
Atorvastatin	40 mg	1 by mouth every evening	HLD				80%
Amiodarone	200 mg	2 by mouth tablets (400 mg) twice a day for 7 days, then 1 tablet (200 mg) twice a day for 7 days, then 1 tablet (200 mg) once a day (14 days total)	Atrial fibrillation				50%
Diltiazem XR	240 mg	1 by mouth daily	Atrial fibrillation				30%
Digoxin	125 mcg	1 by mouth daily	Atrial fibrillation	Non CYP			
Rivaroxaban	20 mg	1 by mouth daily with dinner	Atrial fibrillation				55%
Olmesartan	40 mg	1 by mouth daily	HTN	Non CYP			
Furosemide	20 mg	1 by mouth daily	Fluid retention	Non CYP			
Liraglutide	0.6 mg	1 injection under the skin daily	T2DM	Non CYP			
Metformin	850 mg	1 by mouth twice daily	T2DM	Non CYP			
Pregabalin	75 mg	1 by mouth twice daily	Nerve pain	Non CYP			
Fluticasone nasal spray	50 mcg/act	2 sprays per nostril daily	Seasonal allergies	Non CYP			
Tamsulosin	0.4 mg	1 by mouth daily	BPH			25%	60%
Zolpidem	5 mg	1 by mouth every evening as needed	Sleep		22%		61%
Cephalexin	500 mg	1 by mouth twice daily	Joint infection (prosthetic knee)	Non CYP			

Weak substrate	Medium Substrate	Strong substrate	Inhibitor	Non CYP/Undetermined
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Key: mg = milligram; mL = milliliter; act = actuator; mcg = microgram; XR = extended release; HLD = hyperlipidemia; BPH = benign prostate hypertrophy; T2DM = type 2 diabetes mellitus; * indicates a prodrug.

Initial Consultation Outcomes: The clinical pharmacist reconciled the medication list and assessed for clinical appropriateness and medication safety considerations using an advanced clinical decision support system (CDSS; MedWise™) within one-week post-discharge. The CDSS allowed the pharmacist to consider multiple medication characteristics, cytochrome P450 interactions, risk of drug-induced long QT syndrome, anticholinergic burden, and sedative burden. Ultimately, the pharmacist aimed to decrease the medication risk score to improve medication safety. First, the pharmacist noted that the patient was prescribed a subtherapeutic dose of liraglutide 0.6 milligrams per day for blood glucose management. Given the patient’s controlled glycosylated hemoglobin level of 6.7%, the pharmacist advised the primary care provider to reassess the need for continued use. Per the package insert, liraglutide is initiated at 0.6 mg for one week to avoid gastrointestinal symptoms; however, it does not provide

effective glycemic control at this dose [3].

Instead, the pharmacist advised the patient to follow a healthy diet rich in whole grains, vegetables, and protein. Considering the patient had HFpEF, the pharmacist also recommended a routine walking exercise aligned with provider guidance [4].

Next, given the presence of CHF, the pharmacist also advised the provider to prioritize discontinuation of diltiazem using a tapered schedule over several weeks. Instead, the pharmacist advised the provider to initiate a cardio-selective beta-blocker in a few weeks after the taper, such as bisoprolol, to mitigate the risk of peripheral edema, negative inotropic effects, and mortality associated with diltiazem use [5]. The pharmacist advised the provider to monitor closely for reduced effectiveness of beta-agonist therapy.

Then, upon assessment for high-risk medications in the elderly,

the pharmacist advised the primary care provider to consider discontinuation of zolpidem due to its ability to increase the risk of delirium or complex sleep behaviors [6]. Instead, the pharmacist advised the primary care provider to taper off zolpidem and trial low dose melatonin as a safer anti-insomniac alternative, but only if the patient was still experiencing insomnia. Melatonin is known to have a sedative activity; hence, the patient was instructed to be cautious and use precautions if getting out of bed in the middle of the night to prevent falls once they started melatonin treatment.

The patient reported stable blood pressure and heart rate readings during the initial consultation; hence, the pharmacist advised the cardiologist to prescribe sublingual nitroglycerin as needed for angina post-MI [7]. Next, they recommended close monitoring for bleeding complications given the presence of triple therapy. Additionally, they recommended discontinuation of prasugrel and initiation of ticagrelor instead, given the patient's age and other contraindications [8]. Lastly, the pharmacist recommended an

immediate 50% reduction in the maintenance dose of digoxin and close monitoring of digoxin levels given the presence of amiodarone [9].

The pharmacist also recommended immediate discontinuation of atorvastatin, a moderate affinity substrate of CYP3A4, to eliminate the major drug interaction with amiodarone. Instead, the pharmacist advised the provider to initiate rosuvastatin, a moderate affinity substrate of CYP2C9, for secondary prevention. By changing the hydroxymethylglutaryl-coenzyme A reductase inhibitor, the pharmacist aimed to mitigate the risk of ADEs, such as rhabdomyolysis [10]. The pharmacist also recommended gabapentin as a more affordable alternative to pregabalin.

Follow-Up Consultation Outcomes: During a follow-up consultation four weeks later, the pharmacist reconciled the medication list (Table 2).

Table 2: Medication List and Summary of Affinity and CYP450 Metabolic Pathways Post-Pharmacist Consultation.

Drug	Dose	Frequency	Indication	1A2	2C9	2C19	2D6	3A4
Aspirin	81 mg	1 by mouth every evening	Stroke prevention	Non CYP				
Ticagrelor	90 mg	1 by mouth twice daily	Stroke prevention					86%
Rosuvastatin	20 mg	1 by mouth daily with dinner	HLD		10%			
Bisoprolol	10 mg	1 by mouth once a day	Atrial fibrillation					40%
Digoxin	125 mcg	1 by mouth daily	Atrial fibrillation	Non CYP				
Rivaroxaban	20 mg	1 by mouth every evening	Atrial fibrillation					55%
Olmesartan	40 mg	1 by mouth daily	HTN	Non CYP				
Furosemide	20 mg	1 by mouth daily	Fluid retention	Non CYP				
Metformin	850 mg	1 by mouth twice daily	T2DM	Non CYP				
Gabapentin	300 mg	1 by mouth in the morning and 2 at night	Neuropathy	Non CYP				
Fluticasone nasal spray	50 mcg/act	2 sprays per nostril daily	Seasonal allergies	Non CYP				
Tamsulosin	0.4 mg	1 by mouth daily	BPH				25%	60%
Melatonin	5 mg	1 by mouth at bedtime	Sleep	60%		30%		
Nitroglycerin	0.4 mg	1 by mouth as needed	Angina	Non CYP				

Weak substrate **Medium Substrate** **Strong substrate** **Inhibitor** **Non CYP/Undetermined**

Key: mg = milligram; mL = milliliter; ac t= actuator; mcg = microgram; T2DM = type 2 diabetes mellitus; HTN = hypertension

The provider accepted all of the pharmacist's recommendations over the course of several weeks.

1. Discontinued liraglutide due to optimal biomarkers and implemented lifestyle modifications to manage T2DM.
2. Discontinued diltiazem and initiated bisoprolol to mitigate the risk of negative inotropic effects and decreased ventricular ejection fraction.
3. Discontinued prasugrel and initiated ticagrelor.
4. Added sublingual nitroglycerin.
5. Discontinued zolpidem and initiated melatonin instead.
6. Discontinued atorvastatin and initiated rosuvastatin instead.

In addition, the provider tapered off amiodarone as ordered on discharge and monitored accordingly. Through these

interventions, the MedWise™ Risk Score [11,12] (medication risk score) decreased in severity from a high-risk score (20) to a low-risk score (11); as this medication score is associated with medication-related ADEs, a decrease in the medication risk score is expected to decrease the risk of ADEs [12].

Discussion

During the initial consultation, the pharmacist identified several drug interactions associated with the cytochrome P450 (CYP) enzymes CYP3A4, CYP2D6, and CYP2C9, and P-gp.

Amiodarone: The anti-arrhythmic amiodarone is metabolized and eliminated through the liver. More specifically, this medication is an inhibitor of multiple CYP450 isoforms, including CYP1A2,

CYP2C9, and CYP2D6 [13]. It is also a high-affinity substrate of the CYP3A4 isoform. When the activity of an isoform is inhibited, all other medications metabolized by the same isoform can be affected, which leads to poorer and unintended clinical outcomes [14]. In this scenario, atorvastatin is a substrate of CYP3A4, but amiodarone acts as a competitive inhibitor of CYP3A4. Thus, when taken with amiodarone, atorvastatin is not metabolized as efficiently (decreased clearance), leading to greater concentrations of atorvastatin in the system. Concomitant use of these drugs also would have increased the patient's risk for myopathy and rhabdomyolysis [9].

Digoxin: The use of digoxin with amiodarone may increase the systemic concentrations of digoxin. Digoxin is a substrate for P-glycoprotein (P-gp), which is an efflux pump responsible for the renal excretion of the drug through tubular secretion [15]. Amiodarone inhibits P-gp, which prevents digoxin from being secreted, leading to increased plasma concentrations [16]. In this scenario, the medication dose prior to the pharmacist's consultation could have led to digoxin toxicity, given the recent initiation of amiodarone. Hence, it was imperative to closely monitor digoxin levels during concomitant therapy with amiodarone. It is important to note that due to amiodarone's long half-life, digoxin dose reductions are often required for some time once amiodarone is discontinued [13].

Diltiazem: Similar to amiodarone and atorvastatin, diltiazem is also metabolized by CYP3A4. However, diltiazem has the same affinity as amiodarone for this isoform. In this scenario, the result of the interaction depended on the order in which the patient took the medications. If diltiazem had been administered hours prior to amiodarone, the metabolism of amiodarone would have been lower [17]. Diltiazem and digoxin are both substrates for P-gp. In this scenario, if the patient had administered both medications concomitantly, it would have increased the risk of bradycardia and AV block, which are synergistic cardiac effects shared by both drugs [18–20]. Hence, it was recommended to discontinue diltiazem and prescribe an alternative agent to mitigate these risks.

Prasugrel: Triple therapy consisting of two anti-platelets and one anticoagulant can be used in patients with atrial fibrillation that undergo percutaneous coronary intervention. However, there is evidence that dual antiplatelet therapy plus a direct oral anticoagulant increases the risk of bleeding and is non-superior to a single antiplatelet plus direct oral anticoagulant [21]. Currently, research is being conducted to reassess the duration of antiplatelet therapy and to determine if ticagrelor or prasugrel alone prevents ischemic events, as well as dual-antiplatelet therapy [22]. The antiplatelet drug prasugrel is a prodrug that the body completely hydrolyzes to an inactive intermediate metabolite. That inactive metabolite is then converted to an active metabolite by CYP3A4 and CYP2B6. For this patient, however, the presence of amiodarone and diltiazem would prevent, at

least partially, prasugrel from converting to the active metabolite. Thus, the pharmacist recommended discontinuing prasugrel and initiating an alternative antiplatelet, such as ticagrelor, that does not require activation [23].

Ticagrelor: Following the proposed changes in the drug regimen, the pharmacist recommended monitoring for ADEs related to bisoprolol, rivaroxaban, and tamsulosin. These three medications are substrates of CYP3A4. Ticagrelor has the greatest affinity of these three, and dose separation to mitigate this interaction was not feasible, given its twice-daily dosing.

Conclusion

The pharmacist's clinical recommendations may have helped avoid hospital readmission related to heart block, diabetes, and potentially delirium through interventions designed to mitigate drug interactions associated with medication-related morbidity.

References

1. Ballinghoff T, Bain KT, Matos A, Bardolia C, Turgeon J, Amin NS. Opioid response in an individual with altered cytochrome P450 2D6 activity: implications of a pharmacogenomics case. *Clin Case Rep J*. 2020;1(6):1–4.
2. Beijer HJM, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci*. 2002;24(2):46–54.
3. Victoza (liraglutide). Plainsboro, NJ: Novo Nordisk Inc; 2020.
4. American Diabetes Association. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020; 43(Suppl 1):S48–S65.
5. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21): e1–e76.
6. American Geriatrics Society. Updated AGS beers criteria[®] for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694.
7. Amsterdam EA, Wenger NK, Brindis RG, Jr Casey DE, Ganiats TG, Jr Holmes DR, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64(24):e139–e228.
8. Dewilde WJM, Oirbans T, Verheugt FWA, Kelder JC, De Smet BJGL, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381(9872):1107–1115.

9. Winter ME. Drug Monograph Digoxin. Basic Clinical Pharmacokinetics. 4th ed. Lippincott Williams & Wilkins;2003.
10. Franz CC, Bruggisser M, Krähenbühl S, Bravo AER. Rhabdomyolysis associated with atorvastatin combined with amiodarone and fluconazole. *Praxis (Bern 1994)*. 2011;100(5):273–284.
11. US Trademark Registrations. Medwise. Tabula Rasa Healthcare, Inc; 2020.
12. Bankes DL, Jin H, Finnel S, Michaud V, Knowlton CH, Turgeon J, et al. Association of a novel medication risk score with adverse drug events and other pertinent outcomes among participants of the programs of all-inclusive care for the elderly. *Pharmacy (Basel)*. 2020; 8(2):87.
13. McDonald MG, Au NT, Rettie AE. P450-Based Drug-Drug Interactions of Amiodarone and its Metabolites: Diversity of Inhibitory Mechanisms. *Drug Metab Dispos*. 2015; 43(11):1661–1669.
14. Deodhar M, Al Rihani SB, Arwood MJ, Darakjian L, Dow P, Turgeon J, et al. Mechanisms of CYP450 Inhibition: Understanding Drug-Drug Interactions Due to Mechanism-Based Inhibition in Clinical Practice. *Pharmaceutics*. 2020;12(9):846.
15. Cavet ME, West M, Simmons NL. Transport and epithelial secretion of cardiac glycoside, digoxin, by human intestinal epithelial (Caco-2) cells. *Br J Pharmacol*. 1996;118(6):1389–1396.
16. Amiodarone (Cordarone) product package insert. Wyeth Pharmaceuticals Inc. Philadelphia: PA;2015.
17. Lee JY, Lee SY, Oh SJ, Lee KH, Jung YS, Kim SK. Assessment of drug-drug interactions caused by metabolism-dependent cytochrome P450 inhibition. *Chem Biol Interact*. 2012;198(1–3):49–56.
18. Rameis H, Magometschnigg D, Ganzinger U. The diltiazem-digoxin interaction. *Clin Pharmacol Ther*. 1984;36(2):183–189.
19. Jones WN, Kern KB, Rindone JP, Mayersohn M, Bliss M, Goldman S. Digoxin-diltiazem interaction: a pharmacokinetic evaluation. *Eur J Clin Pharmacol*. 1986;31(3):351–353.
20. Mahgoub AA, El-Medany AH, Abdulatif AS. A comparison between the effects of diltiazem and isosorbide dinitrate on digoxin pharmacodynamics and kinetics in the treatment of patients with chronic ischemic heart failure. *Saudi Med J*. 2002;23(6):725–731.
21. Peterson BE, Bhatt DL. Management of anticoagulation in patients with atrial fibrillation undergoing pci: double or triple therapy? *Curr Cardiol Rep*. 2018;20(11):110.
22. Capodanno D, Huber K, Mehran R, Lip GYH, Faxon DP, Granger CB, et al. Management of antithrombotic therapy in atrial fibrillation patients undergoing pci: jacc state-of-the-art review. *J Am Coll Cardiol*. 2019;74(1):83–99.
23. Effient (prasugrel) product package insert. Eli Lilly and Company. Indianapolis; 2019.