

*Drug interactions in an elderly patient with significant polypharmacy
A Case study; Described by the use of YouScript software and compared to Epocrates*

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Introduction:

Polypharmacy is a problem of growing interest in geriatrics with the increase in drug consumption in recent years, particularly among people aged > 65 years^{6, 20}. The main reasons for the use of polypharmacy are: longer life expectancy, co-morbidity and the implementation of evidence-based clinical practice guidelines. However, polypharmacy also has important adverse consequences, such as induced risk of adverse drug reactions and a decline in medication efficacy due to reduced compliance¹³. These drug interactions can become a significant problem and increase the risk of health complications when administered in patients with genetic susceptibility. These risks can be reduced with personalized medicine by the proper use of drug interaction software and genetic characterization.

Polypharmacy increases the risk of an adverse drug reaction (ADR) in elderly patients mainly due to the weakening and ageing of metabolic pathways⁸. Studies from the Japan Geriatric Society have shown that polypharmacy and renal impairment are prevalent conditions amongst elderly patients admitted through an acute assessment unit (AAU)¹⁰. In these elderly patients, polypharmacy is attributable to greater comorbidities and is associated with an increased risk of adverse consequences²⁶.

A retrospective study of 200 admissions to an AAU in Australia examined the risk factors and consequences associated to polypharmacy in the geriatric population (>65 years old)²⁶. The study showed that medications for cardiovascular disease (46%) and nervous system (30%) involved the bulk of these patients chronic pharmacotherapy. 81% of these patients were taking five or more medications concurrently, at the time of hospital admission. The presence of more than two comorbidities (OR=6.80, p<0.001) and age (OR=2.91, p=0.01) were strong factors associated with polypharmacy. Excessive polypharmacy was associated with an increased risk of prescription errors that could cause temporary harm or required intervention (OR=5.23, p=0.009), but was not associated with a prolonged length of stay²⁶.

Adverse effects of polypharmacy can be improved with the advent of online algorithmic tools for rapid assessment of possible ADR in patients with relative poor or enhanced metabolism. Physicians on site commonly use several online tools that lack the power and capability of including personalized patient information with their genetic variability. Recently, special attention has been given to gene-specific pharmacokinetic polymorphisms that may cause ADR and fluctuations in expected systemic drug concentrations with the associated side effects. This discovery has led to the development of new strategies that cater to the specific genome burden of that particular individual; specially in high risk populations such as those that: require multiple chronic concurrent drug therapies, require drugs with low therapeutic indexes, have multiple comorbidities

and/or have impaired renal function. Individuals without these risk factors are not exempt of these metabolic fluctuations, but they are most likely to have sub-clinical derangements that are not amenable to be assessed for clinical impact. Therefore, this case reports a very high-risk patient representing a commonly affected hospital population with likely sub-optimal pharmacotherapy that would benefit from the proper individualized drug reconciliation. We introduce the example case of how YouScript online tool²⁷ could aid in managing drug reconciliation recommendation at hospital discharge, and compare the quality of the information acquired with this tool to other similar commercially available tools. The main objective of this case report is to promote the re-evaluation of our current approaches towards the personalized management of long-term pharmacotherapy in elderly patients with multiple chronic illnesses.

Case Report:

Chief complaint

Patient visits the nephrology clinics because he experiencing frequent nausea and vomiting symptoms

Background

A 75 y/o male with PMHx of: CKD stage IV secondary to uncontrolled hypertension, CAD, S/P CABG x 2 (2010), DM type II, U-HTN and CVA (2010). This patient was in his usual state of health which consists of: independent ADLs, ambulation and administering his meds for his chronic ailments w/o significant complications until he visited the Nephrology Clinic due to nausea and vomit symptoms. At that time the patient referred fatigue, unintended weight loss of 40lbs in approximately 2 months with associated twice-weekly vomits consisting mainly of gastric contents without any evidence of blood and diarrhea every other day. Stool is brownish with fluid, but not malodorous, dark or grossly bloody. Upon admission, patient was found with electrolyte imbalances and was transferred for further evaluation. Patient denied: cough, chills, orthopnea, nocturnal paroxysmal dyspnea, SOB or chest pain. The patient also denied: insomnia, pruritus, weakness or palpitations. Patient was admitted on Nephrology Ward for medical treatment with potassium binders, Bicitra and IV fluids. Urine spots ordered and Nephrology consult was placed. On 12/4/11, the patient developed unstable angina and was treated according to available guidelines. Patient allergic to Penicillin and has no acute distress upon physical examination.

Relevant Present and Past Medical History

DM type II	S/P CVA (2010)	Short-term memory loss
CKD stage IV	Chronic Sinusitis	Pseudophakia B/L (1998)
Uncontrolled HTN	Bronchial asthma	Depression (self-referred)
CAD (S/P CABG x 2)	Primary hypertriglyceridemia	

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Outpatient Meds:

1. Insulin 70 U (basal)/ 30 U (short)
2. Procardia XL 60mg PO qd
3. ASA 81mg PO qd
4. Allegra D PO bid
5. Avapro 500mg PO qd
6. Vasotec 20mg PO bid
7. Gemfibrozil 600mg PO before meal pm
8. Albuterol 2.5 mg bid by personal nebulizer

Toxic Habits

Denies any toxic habits such as alcohol abuse

Relevant Family History

Refers only family hx for diabetes mellitus type II on mothers side & MI of an uncle relative that died very young.

Relevant laboratories and imaging studies

ECG (Upon admission on 11/29/11)

Impression:

- 56 bpm, sinus bradycardia, acute ischemic changes consistent with inferior and lateral infarcts, second degree AV block type I.

Blood chemistries (11/29/11):

- | | |
|---|-------------------------|
| - CO ₂ : 21 mEq/L (mild low) | - Cr: 2.9 mEq/L (high) |
| - BUN: 54 mEq/L (high) | - Glu: 132 mEq/L (high) |

Blood chemistries (12/7/11)

- | | | |
|------------------------|------------------------|-----------------------|
| - BUN: 61 mEq/L (high) | - Glu: 125 g/dL (high) | - Tot Prot: 4.10 g/dL |
| - Cr: 3.19 g/dL (high) | - Alb: 2.0 g/dL (low) | (low) |

U/A (12/7/11):

- | | | |
|---------------------------|-------------------------|--------------------------|
| - Prot: 500 mg/day (high) | - UNa: 21 mEq/day (low) | - UUrea: 436 g/dL (high) |
| - Glu: 50 g/day (high) | - UCr: 97 mg/kg/day | |
| - RBC: 15-20 hpf (high) | (very high) | |

Immediate pharmaco-therapeutic treatment:

1. Lactulose, kayexalate, PhosLo, Coreq and Bicitra; to correct electrolytes and Acidosis.
2. Insulin SQ daily for hyperglycemia

3. Administered Heparin for DVT prophylaxis
4. Ranitidine for GI prophylaxis

YouScript algorithm and discussion of outcome

Clinical reports will often provide data on expected range of increase or decrease in concentration of specific drug-drug interactions. When there are clinical reports of an interaction, but they do not allow a quantitative prediction, the words: “some” or “major” are shown accompanied by + or – sign for direction of change, most often when interaction is not pharmacodynamic. There are many clinical reports about interactions between pairs of drugs. Unfortunately, reports of interactions among multiple drugs are rare and this is when this program’s algorithmic database is truly valuable. YouScript will account for: narrow therapeutic indexes, pro-drug and drug metabolism, and both mechanism-based and competitive interactions. However, a disclaimer has been issued that this program is not designed to diagnose, treat or make decisions for the clinician and should only be employed as a valuable tool in the objective appraisal of potential interactions for periodic drug reconciliation in patients with multiple concurrent medications. A task usually reserved for experienced pharmacologists, which are scarcely available in the general clinical setting. The following list of medications were being previously prescribed: insulin Procardia XL, aspirin, Allegra D, Avapro, Vasotec, gemfibrozil, albuterol; and others added inpatient: lactulose, kayexalate, PhosLo, Coreq, Bicitra, heparin and ranitidine.

Upon introducing the list of medications (see list above) being administered to the patient at that moment and looking into ADRs using the software described above, the resulting layout shown in Table 1 was obtained.

Table 1: Drug interactions before YouScript-aided Drug Reconciliation²⁷

Clinical Impact	Causative Agent	Evidence
<u>simvastatin acid</u> (Zocor's active metabolite)	Major	<u>gemfibrozil</u>
<u>gemfibrozil</u>	Major	<u>simvastatin acid</u> , <u>Zocor</u>
<u>albuterol inhalation</u>	Major	<u>labetalol</u> , <u>digoxin</u> , <u>Lasix</u>
<u>Zocor prodrug</u>	Major	<u>gemfibrozil</u> , <u>Lasix</u> , <u>Vasotec</u> , <u>aspirin</u> , <u>metabolite enalaprilat</u>
<u>digoxin</u>	>200% + Major >N<	<u>Lasix</u> , <u>labetalol</u> , <u>aspirin</u> , <u>hydralazine</u> , <u>albuterol inhalation</u> , <u>Procardia XL</u> , <u>clonidine</u>
<u>labetalol</u>	Major	<u>Avapro</u> , <u>Lasix</u> , <u>metabolite enalaprilat</u> , <u>Procardia XL</u> , <u>clonidine</u> , <u>digoxin</u> , <u>aspirin</u> , <u>Vasotec</u> , <u>albuterol inhalation</u> , <u>insulin</u>
<u>metabolite enalaprilat</u> (Vasotec's active metabolite)	Some	<u>labetalol</u> , <u>Lasix</u> , <u>aspirin</u> , <u>Zocor</u>

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<u>Avapro</u>	 Some	<u>labetalol</u> , <u>aspirin</u> , <u>insulin</u> , <u>Lasix</u>
<u>Vasotec prodrug</u>	 Some 	<u>labetalol</u> , <u>insulin</u> , <u>Lasix</u> , <u>aspirin</u> , <u>Zocor</u>
<u>insulin</u>	 None	<u>Vasotec</u> , <u>Avapro</u> , <u>clonidine</u> , <u>labetalol</u> , <u>gemfibrozil</u>
<u>Procardia XL</u>	 None	<u>labetalol</u> , <u>hydralazine</u> , <u>aspirin</u> , <u>clonidine</u>
<u>aspirin</u>	 None	<u>Vasotec</u> , <u>metabolite enalaprilat</u> , <u>hydralazine</u> , <u>Avapro</u> , <u>Lasix</u> , <u>Zocor</u>
<u>Allegra</u>	 None	
<u>sodium citrate (from Bicitra)</u>	 None	
<u>Phoslo Gelcaps</u>	 None	
<u>clonidine</u>	 None	<u>labetalol</u> , <u>insulin</u> , <u>Procardia XL</u> , <u>digoxin</u>
<u>hydralazine</u>	 None	<u>Procardia XL</u> , <u>aspirin</u> , <u>digoxin</u>
<u>Lasix</u>	 None	<u>digoxin</u> , <u>labetalol</u> , <u>metabolite enalaprilat</u> , <u>Vasotec</u> , <u>Zocor</u> , <u>aspirin</u> , <u>Avapro</u> , <u>albuterol inhalation</u>
<u>citric acid (from Bicitra)</u>	Metabolism unknown	

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This drug cocktail at the time of patient's discharge includes: 11 cardiovascular drugs [post-MI (3), HTN (6) and dyslipidemia (2)], 2 drugs for renal complaints and 3 for: asthma, insulin-dependent diabetes mellitus and chronic sinusitis.

There were a total 16 medications for long-term use with a shocking predominance of cardiovascular pharmacotherapy as predicted by the Japan Geriatric Society²⁶. When these 16 drugs were evaluated the outcome targeted 6 drugs (Simvastatin, gemfibrozil, Zocor, digoxin, albuterol and labetalol) as severely interacting with others (see red flagged list in table 1 above); one of these shows interaction with both the pro-drug and active drug form.

The major interaction in this case is due to gemfibrozil, which causes Zocor pro-drug and simvastatin acid to sharply accumulate. The Zocor pro-drug needs to be metabolized to simvastatinic acid in order to produce the desired systemic effects, which was evident by the substantial atherosclerotic disease. This pro-drug has the same metabolic route as simvastatinic acid, but has a more extended metabolism through CYP3A4 which accounts for close to 66% of the drug metabolized (see table 2).

Table 2 : Zocor prodrug metabolism²⁷

Zocor prodrug		Major		gemfibrozil, Lasix, Vasotec, aspirin, metabolite enalaprilat	Notes #4 Prod. Insert
Affected Drug	AUC will go..	because of ...	and the mechanism is ...		
Zocor prodrug [A]	↑ Insignificant	Procardia XL	CYP3A4		
"[A]	↑ Insignificant	hydralazine	CYP3A4		
"[A]	↑ Explain? Insignificant	gemfibrozil	CYP2C8		
"[A]	↓	aspirin	ABCB1- P-gp		

Increased pro-drug results in sub-therapeutic levels of simvastatinic acid and hence may affect this patient's frail condition adversely; increasing the probability for unstable angina, acute myocardial infarction, cerebro-vascular accidents and peripherovascular disease, all of which may prove to be fatal. Currently there is no commercially available simvastatinic acid drug in order to bypass the pro-drug. Nevertheless, even when administering simvastatinic acid (active drug) it will interact extensively with: Procardia XL, hydralazine and gemfibrozil, through inhibition of: CYP2C8 and CYP3A4, which together account for more than 75% of this drug's metabolism. So, if both Zocor and simvastatinic acid are mainly metabolized through CYP3A4, the levels of both drugs should be expected to increase due to inhibition of this common metabolic route.

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The results of this unexpected active drug increase sustained for a long-term period may result in dreaded statin toxicity that may result in: abdominal pain, diarrhea, indigestion, and a general feeling of weakness. Less common side effects include: joint pain, memory loss and muscle cramps²⁷; cholestatic hepatitis, hepatic cirrhosis, rhabdomyolysis and myositis, which have been reported in patients receiving the drug chronically^{4,2}.

*ADR evaluation for digoxin reveal that it may increase up to two-fold the original intended level (200%) in the blood due to inhibition of glucuronidation, which is its major metabolic route²⁷ (see table 1). **The program flags this interaction as the most severe and dangerous of all interactions.** Digoxin also has a very narrow therapeutic index with therapeutic concentrations ideally maintained between 0.5 - 0.8 ng/mL, which means that a small increase in blood serum levels may lead to toxic or lethal side effects¹. In a renal patient, the available clinical reports have insisted on regular monitoring of serum electrolytes to screen for reduced potassium levels because increased digitoxicity is frequently observed in this setting¹³. However, this patient arrives with a substantial hyperkalemia (as a result of his renal disease) and is administered potassium binders to lower these dangerously high levels of potassium. Therefore, this treatment may also predispose him to digoxin toxicity if not carefully monitored. Digoxin toxicity includes: fatigue, blurred vision, "yellow vision", anorexia, nausea, vomiting, diarrhea, abdominal pain, headache, dizziness, confusion, delirium. Characteristic EKG changes include bradycardia, which is the most frequent vital sign abnormality in toxicity, and a prolonged PR interval¹². Also, when digitalis glycosides used in combination with beta-blockers (Labetalol) they work together to slow atrioventricular conduction and decrease heart rate^{9,1}. Our patient's EKG is notable for sinus bradycardia and 2nd degree heart block (prolonged PR interval) that merit further evaluation in this setting of possible drug interactions.*

The 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines have recommended against routine use of digoxin in CHF since 1997 as it does not: improve prognosis, lower mortality, or slows disease progression⁹. Digoxin may be used for symptomatic relief in patients with substantially reduced ejection fraction in acute exacerbations of disease under medical vigilance for side effects and ADRs.

Labetalol is a non-cardioselective beta-blocker used for: rate control, decrease blood pressure and lower myocardial oxygen demand. According to the product label, this drug is contraindicated in asthmatic patients under albuterol treatment because it may potentiate asthmatic events²⁷. However, in this patient both medications were co-administered and both drugs were flagged with ADR (see table 1). Labetalol and digoxin are mainly metabolized by *glucuronidation*, which is inhibited by Procardia and aspirin (table 3) and therefore predisposed to increase the blood levels of labetalol.

Table 3: Labetalol metabolism²⁷

 labetalol	 Major	Avapro, Lasix, metabolite enalaprilat, Procardia XL, clonidine, digoxin, aspirin, Vasotec, albuterol inhalation, insulin	Notes #5 Prod. Insert
Affected Drug	AUC will go..	because of ...	and the mechanism is ...
labetalol 	 Insignificant	Procardia XL	
" 	 Insignificant	aspirin	

Contributing to this patient’s sinus bradycardia, a meta-analysis concluded that beta-blockers used for the treatment of hypertension are associated with increased risk for new-onset diabetes mellitus, hypertriglyceridemia, bronchial asthma exacerbations, higher baseline blood sugar and masks hypoglycemic state^{3, 23}. The patient’s history of MI and uncontrolled hypertension currently requires multiple combined anti-hypertensive drugs for long-term management. Moreover, some recent studies have argued against *routine beta-blocker* use in patients with hypertension despite current guidelines, especially when comorbid contraindications are present¹⁵.

*The most recent reports of the Joint National Committee (JNC VI) and the World Health Organization recommend beta-blockers and diuretics as first-line therapy for uncomplicated essential hypertension^{11, 25}. Similar recommendations have been issued over the past few years by many authoritative sources and research published in influential journals. These recommendations were supposedly based on multiple prospective randomized trials attesting that only beta-blockers and diuretics, both in monotherapy and combined, reduced morbidity and mortality in hypertension. Ever since the Veterans Administration study in the 1970s¹⁸, multiple and prospective randomized trials have documented that diuretic-based therapy reduces the risk of stroke and, to a lesser extent, of heart attacks and cardiovascular morbidity and mortality. However, the data are much less convincing for beta-blockers¹⁶. In fact, no trial has shown that lowering blood pressure with a beta-blocker reduces the risk of a heart attack or cardiovascular event in patients with essential hypertension compared with placebo. In contrast, several prospective studies are now available showing that blood pressure reduction with **calcium channel blockers** diminishes cardiovascular morbidity and mortality and, at least in meta-analysis, all-cause mortality. Therefore, this patient should benefit from stroke prevention and anti-hypertensive effects of diuretics (i.e. Lasix) and optimize antihypertensive therapy with current medications, but avoiding the use of beta-blockers.*

We also find 100% inhibition of gemfibrozil metabolism when concurrently administered with both: Procardia XL and aspirin since gemfibrozil is also metabolized through glucuronidation (table 4). Fibrates are a mainstay in treating patients with a substantial hypertriglyceridemic lipid abnormality. Seems logical to reconsider alternative therapy or adjust doses and follow up with drug serum levels and lipid panels.

Table 4: Gemfibrozil metabolism²⁷

gemfibrozil		Major	simvastatin acid, Zocor, insulin	Notes #2 Prod. Insert
Affected Drug	AUC will go..	because of ...	and the mechanism is ...	
gemfibrozil [A]	↑ Insignificant	Procardia XL	UGT2B7	
* [A]	↑ Insignificant	aspirin	UGT2B7	

Drug reconciliation

Since the ADR profile was significant and as many a five different drugs and a pro-drug showed significant concern (table 1); we reevaluated the list of medications and considered some alternate approaches. Drug reconciliation considerations in this patient included researching guidelines for alternative therapy and substituting drugs within a same family, but with different metabolic routes. Dose adjustments are always possible in all patients with assumed borderline toxic levels or sub-therapeutic doses, but this is usually clinically determined and regular measurement of multiple drug levels for periodic optimization is neither practical, nor economically feasible. However, we emphasize the importance of drug measurements and monitoring as a research tool for positive confirmation and metabolic feedback analyses. In the absence of specific drug information to confirm software predictions, we utilize the online tool to design new drug treatments in order to minimize ADIs and reduce possible drug interactions and changing this individual’s outpatient drugs (table 5). These recommendations do not include any genetic profiling information, *which could also be critical to ADR evaluation.*

Table 5: Recommended drug list for pharmacotherapy after ADR evaluation²⁷

	Delete All	CONTINUE	STARTING	STOPPING
<input checked="" type="checkbox"/> insulin		●	○	○
<input checked="" type="checkbox"/> Procardia		●	○	○
<input checked="" type="checkbox"/> Allegra		●	○	○
<input checked="" type="checkbox"/> Avapro		●	○	○
<input checked="" type="checkbox"/> Vasotec		●	○	○
<input checked="" type="checkbox"/> gemfibrozil		●	○	○
<input checked="" type="checkbox"/> albuterol inhalation		●	○	○
<input checked="" type="checkbox"/> Zocor		○	○	●
<input checked="" type="checkbox"/> digoxin		○	○	●
<input checked="" type="checkbox"/> clonidine		○	●	○
<input checked="" type="checkbox"/> hydralazine		○	●	○
<input checked="" type="checkbox"/> Lasix		○	●	○
<input checked="" type="checkbox"/> labetalol		○	○	●
<input checked="" type="checkbox"/> Bicitra		○	●	○
<input checked="" type="checkbox"/> Phoslo Gelcaps		○	●	○
<input checked="" type="checkbox"/> aspirin		○	○	●
<input checked="" type="checkbox"/> epoetin alfa injection		○	●	○

Other algorithmic resources have been available for quite a while and are easily found on the web. However, the quality of the information obtained by these other programs do not include the following, 1) the multiple specific metabolic routes affected, 2) expected change in drug concentration, and 3) drug/prodrug interactions. This provides valuable criteria for patient management and reassessment. One of the most used software by physicians to look for ADRs when contemplating pharmacotherapy is *Epocrates*. In order to perform a quick comparison between these two tools we employed this Multi-Drug Checker online and found that the program flagged 22 drug interactions for this case. There was 1 contraindication for gemfibrozil plus statin use, and 4 recommended avoidance of drugs that predominantly interacted with Labetalol. Organized in a somewhat unfriendly manner, it arranges individual drug interactions by severity of the interaction (see table 6).

Table 6: Multi- Drug Checker from Epocrates²⁸

EPOCRATES® ONLINE

MultiCheck List

albuterol inhaled
Allegra Allergy 24 Hour
aspirin
Avapro
Bicitra
clonidine
digoxin
epoetin alfa
gemfibrozil
Humulin R
hydralazine
labetalol
Lasix
PhosLo
Procardia XL
Vasotec
Zocor

MultiCheck Results

Contraindicated

1. gemfibrozil <-> Zocor

contraindicated: combo may incr. simvastatin levels, risk of myopathy, rhabdomyolysis (hepatic uptake transporter inhibited)

Avoid/Use Alternative

Medscape Drug Interaction checker is a similar Epocrates analogue (table 7). However, results for this algorithm flagged 57 interactions in total. The program does not consider pro-drug metabolism with 1 contraindication for gemfibrozil with statin use, and 3 serious drug interactions that surprisingly did not match any of the Epocrates 4 serious drug interactions. Same format as the Epocrates algorithm; it has the same weaknesses detailed above. These free online tools may be valuable for quick assessments of contraindicated concurrent drug therapy, but are not reliable for in-depth evaluation of pharmacotherapy for long-term drug use and organizing individual records and genetic metabolic profiling for personalized medicine purposes.

Table 7: Drug Interaction Checker from Medscape²⁹

Drug reconciliation proceeded by eliminating the following drugs: Aspirin 81mg, Procardia XL, Digoxin, Zocor and Labetalol; and adding Plavix. Adequate blood pressure control will be achieved by adjusting doses of current antihypertensive therapy (CCB, ACEinh, ARB, etc.) with the notable personalized consideration of beta-blocker avoidance in this diabetic and asthmatic patient with AV block and bradycardia. Also, optimization of CHF therapy should be made with ACE/ARB (Vasotec & Avapro) and diuretics (Lasix) that are 1st line treatment for CHF since 1997, instead of cardiac glycoside derivatives⁹. Other recommendations include: cardiology consult, monitor blood sugar levels, yearly Influenza shot, initiation of erythropoietin analogues in addition to iron-containing vitamins and encourage lifestyle changes to include: exercise, smoking cessation, tight glycemic control and other dietary modifications

Table 8: Drug interactions after YouScript-aided Drug Reconciliation²⁷

Affected Drug	Clinical Impact	Causative Agent
metabolite enalaprilat (Vasotec's active metabolite)	Some	Lasix, Plavix
insulin	Some >N<	Vasotec, clonidine, gemfibrozil
Procardia	Some	Lasix, hydralazine, clonidine
Avapro	Some	Lasix, Plavix

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<u>Vasotec prodrug</u>	Some	<u>clonidine</u> , <u>insulin</u> , <u>Lasix</u> , <u>Plavix</u>
<u>gemfibrozil</u>	Some	<u>insulin</u>
<u>albuterol inhalation</u>	Some	<u>Lasix</u>
<u>clonidine</u>	Some	<u>Lasix</u> , <u>Vasotec</u> , <u>insulin</u> , <u>Procardia</u>
<u>hydralazine</u>	Some	<u>Procardia</u>
<u>Lasix</u>	Some	<u>Avapro</u> , <u>Procardia</u> , <u>clonidine</u> , <u>metabolite enalaprilat</u> , <u>Vasotec</u> , <u>Plavix</u> , <u>albuterol inhalation</u>
<u>Plavix prodrug</u>	Some	<u>Procardia</u> , <u>Avapro</u> , <u>Lasix</u> , <u>Vasotec</u> , <u>metabolite enalaprilat</u>
<u>clopidogrel metabolite (Plavix's active metabolite)</u>	None	
<u>Allegra</u>	None	
<u>sodium citrate (from Bicitra)</u>	None	
<u>Phoslo Gelcaps</u>	None	
<u>citric acid (from Bicitra)</u>	Metabolism unknown	
<u>epoetin alfa injection</u>	Unpredictable change	

Results after outpatient drug reconciliation at the time of hospital discharge confirm the absence of serious interactions and reduce the need for frequent drug level monitoring in this patient. Nonetheless, all patients whose medications have been recently changed or dose-adjusted should be followed for: tolerance, side effects, compliance and therapeutic efficacy.

Case summary:

The case presented here is that of an elderly patient with multiple co-morbidities that was admitted to the Nephrology Ward because of renal complaints. He was under treatment for multiple conditions and taking over 16 different drugs. Moreover, at the time of discharge, the quantity of outpatient medications was close to double that of admission. Upon evaluation of this patient's current pharmacotherapy for drug interaction we found that there were major adverse drug reactions (ADR) among 6 drugs. To circumvent these ADR we determined that drugs concerning this patient's 4 major health concerns (uncontrolled hypertension, CHF, post-MI prophylaxis and hypertriglyceridemia) required appropriate reconciliation. The following drugs needed to be changed, discontinued or optimized: the "baby aspirin" was changed for Plavix as a suitable substitute⁷, elimination of Labetalol for U-HTN, CHF and MI prophylaxis

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^{16,18}, discontinuation of digoxin according to current American Heart Association Task Force on Practice Guidelines⁹, and optimization of current anti-HTN with Procardia XL, Vasotec and Enalapril as per current K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease^{22,30} and recent clinical trials on MI prophylaxis in elderly patients with cardiovascular disease¹⁸.

Insulin and Procardia XL inhibit a glucuronidase enzyme, which is expected to cause an increase in gemfibrozil concentration²⁷. This excess of gemfibrozil is associated primarily to gastrointestinal complaints and gallbladder stones, but fibrates in general are associated with increased risk of bone marrow depression and skeletal muscle destruction with associated disseminated muscular pain and myoglobinuria that lead to acute tubular necrosis and acute renal insufficiency^{31,32}. However, isolated primary hypertriglyceridemia in this patient is best managed by a fibrate at adjusted renal doses with frequent monitoring of CPK levels^{17,5}, a molecule that is released in blood when there is skeletal muscle breakdown². Therefore, Gemfibrozil dose was lowered to account for the resulting increased concentration with insulin. If insufficient control of lipid profile is seen, then the authors of this study, suggest the use of Niaspan, a nicotinic acid (B Vitamin) derivative used for hypertriglyceridemia control in a formulation that is extended release for once daily administration and has been checked through YouScript without any resulting ADR. Patient's Creatinine/BUN ratio, triglyceride levels, blood pressure and blood glucose must be followed for long-term expected adjustments since dosing in the elderly population, specially with CKD and considerable polypharmacy, is frequently erratic and demands close monitoring²².

To avoid inappropriate medication use and improve the quality of prescription we strongly recommended a careful evaluation of all drugs, particularly when there is substantial polypharmacy. Comprehensive geriatric assessment (CGA) has proved effective in reducing the number of prescriptions and daily drug doses for patients by facilitating discontinuation of unnecessary or inappropriately medicated, and screening for unsuitable combinations where possible drug interaction may be a problem²⁶. The most appropriate medication regimen should combine existing evidence-based clinical practice guidelines with data gathered from CGA, including social and economic considerations. Periodical medication review is highly recommended for the elderly, particularly, as the risk or presence of multiple co-morbidities increases. With the advent of individualized medicine and the accessibility for human genomic studies, metabolic algorithms like Youscript Personalized Prescribing System™ have been developed as a novel tool for the management of subjects that require the use of multiple drugs, some of which are essential for life prolongation and may interact heavily or have narrow therapeutic indexes.

Intended pharmacotherapy reconciliation at any clinical setting should be monitored for immediate side effects and carefully readjusted as needed. However, addition of systemic drugs should be attentively evaluated by the primary physician for in-depth assessment of possible interactions, as well as short and long-term side effects that may warrant further changes in

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pharmacological management. Adherence, careful administration and dosing may be an issue in most elderly patients so a careful effort should be made to assess possible adverse drug reactions (ADRs), particularly, due to genetic and metabolic susceptibility.

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