

Data mining results for reduction of adverse drug–drug interaction events in older adults are clinically applicable

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Abstract

Background: Polypharmacy increases the risks of drug–drug interactions (DDIs), which increase the risk of adverse drug events (ADEs). Data mining techniques have described high-order (three or four) drug combinations as high risk for ADE and suggested alternative low-risk combinations, but were not able to establish clinical feasibility.

Objective: The objective of this study is to evaluate the clinical feasibility of potentially low-risk drug combinations identified in previous work through a data mining technique as substitutes for high-risk high-order drug combinations.

Methods: This expert-review study utilizes potentially high-risk high-order drug combinations and complementary low-risk combinations identified in previously published work from Medicare fee-for-service (2018) and MarketScan Medicare Supplemental claims emergency department (ED) data (2012–2020). We convened a panel of clinical experts to adjudicate the list for clinical feasibility. A standard rubric was developed, and the reviewers indicated whether the data-driven substitutions were always, sometimes, or never clinically acceptable and provided comments. Two experts, not involved in the initial panel review, reviewed the results produced by the panel to determine agreement or disagreement among reviewers. The results of this clinical review are presented.

Results: Of the 1904 high-/low-risk combinations reviewed, 606 were deemed always acceptable; 588 were anticoagulant ADEs, 18 were opioid, and none were antidiabetic. The 20 most frequently observed high-risk combinations were all anticoagulant ADEs; 11 of the top 20 involved proton pump inhibitor substitution and 9 involved statin substitutions.

Conclusion: High-risk high-order DDIs with low-risk alternatives as identified in Medicare fee-for-service and MarketScan databases are identifiable, are clinically acceptable, and could decrease ADE-related ED visits.

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Plain language summary

Does a large data set analysis yield clinically appropriate drug substitutions to reduce patient risk?

Large data sets (tens of thousands of observations) can help identify trends that smaller data sets cannot. However, sometimes these trends are artifacts of the large data set and not clinically applicable. We previously used 2 large data sets to identify groups of 3 or 4 drugs that increase patient risk for certain drug side effects in geriatric patients and drugs that could be substituted to decrease these risks. In this manuscript, physicians reviewed

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the suggested drug substitutions to make sure they were clinically possible. We found many substitutions that would be clinically possible and could reduce patient risk for side effects.

Keywords: adverse drug events, anticoagulants, antidiabetic drugs, opioids, physician review

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Introduction

Adverse drug events (ADEs) lead to more than 1.3 million older adult emergency department (ED) visits and 350,000 hospitalizations per year in the United States.¹ High-risk individual medications have been described by the American Geriatrics Society Beers Criteria² and the recent Geriatric Emergency Medicine Safety Recommendations (GEMS-Rx).³ In addition to these individual drug considerations, drug–drug interactions (DDIs) of otherwise appropriate medications are also critical to consider. DDIs occur when the combination of two or more drugs increases the risk for an ADE.

The risk of ADE due to DDIs increases with age⁴ and the number of medications a patient is prescribed.^{5–8} Although most research has focused on two medication combinations, the potential for unrecognized ADEs from the use of ≥ 3 medications, “higher-order drug combinations,” is an area of critical importance.⁹ Identifying appropriate and safer higher-order drug combinations to reduce the use of medication combinations that increase the risk of ADEs would have a direct clinical impact.

In previous work,¹⁰ we applied the mixture drug-count response model to Medicare fee-for-service and MarketScan Medicare supplement data on ED visits to identify higher-order drug combinations with high risk of ADEs as defined by Digmann et al.¹¹ associated with anticoagulants (e.g., gastrointestinal bleeding), antidiabetic drugs (e.g., hypoglycemia), and opioids (e.g., sedation) in older adults. These medication classes were chosen due to established literature regarding two-drug combinations interacting and increasing the risk of ADEs related to these drug classes.^{12–17} This analysis was powerful because it harnessed therapeutic class-based mining to

identify potential ADE-causing high-order DDIs that would go undetected with other methods, and for its ability to suggest alternative lower risk drug combinations. However, this data analytic technique suggests substitutions by drug classes. This results in proposed low-risk drug substitutions that may not be clinically acceptable. For example, it may propose drugs with different modes of delivery within the same therapeutic class that are not interchangeable, such as oral and ophthalmic drops. Therefore, we undertook an expert review of each potential drug substitution to determine the clinical acceptability of the substitutions suggested by the data analytics.

The objective of this study was to determine the clinical feasibility of the high-to-low-risk drug substitutions in three- and four-drug combinations identified through the data mining technique in our previous work.¹⁰

Methods

As described briefly above, our group’s previous work examined 5.1 million ED visits in Medicare fee-for-service and 3.3 million in MarketScan Medicare supplement data to identify high-risk drug combinations associated with anticoagulants, antidiabetic drugs, and opioids in older adults. Briefly, this was a case–control design that identified the high-risk drug combinations based on drug exposure in the 30 days prior to ED visit using the mixture drug-count response model. This prior work identified 1904 high-risk three- or four-drug combinations with a potential low-risk alternative drug combination.¹⁰

The analysis presented here builds upon this large database work. For each three- and four-drug high-risk drug combination with an identified lower-risk combination in previous work

described above, we identified the individual drug substitution(s) to create the lower-risk combination. This reduced the number of substitutions to be reviewed by experts to 286.¹⁰ This study was certified as non-human subjects research by our institutional IRB.

The methodology employed in our previous work¹⁰ relied on drug classes that could result in proposed substitutions that are not clinically feasible, for example, treating antiplatelet and anticoagulant medications as interchangeable. Two investigators (J.C. and K.H.) reviewed all individual drug substitution dyads and removed any that were deemed clearly not acceptable. Reasons a dyad was defined as clearly not acceptable included: medications were different clinical classes (e.g., antiplatelet and anticoagulant) or different modes of delivery that were not clinically interchangeable (e.g., ophthalmologic drops and intravenous).

The two investigators then reviewed the remaining dyads and classified the dyads by the specialty most appropriate for review. They determined that specialists required for review included emergency medicine, cardiology, pulmonology, gastroenterology, endocrinology, and psychiatry. Of note, the medicine subspecialists were also board-certified in internal medicine, which provided an important perspective on medications not specific to a medical subspecialty. Each substitution was reviewed by appropriate specialist(s) in addition to an emergency medicine physician to determine whether the drug substitution suggested by the database analysis was clinically acceptable. Therefore, each substitution was reviewed by at least two reviewers, but no limit was placed on the number of reviewers. Each reviewer indicated if the proposed substitution was always, sometimes, or never clinically acceptable and had the opportunity to provide comments. Each reviewer made this determination based on their clinical expertise. Given knowledge and medication use differences between specialties, disagreements were expected. In cases of disagreement among the initial reviewers, two investigators (J.C. and B.B.) reviewed the selections and comments to make a final determination. In this determination, justified specialty-specific knowledge was favored. For example, if the emergency medicine physician reviewer said something was “always” acceptable, but the cardiologist picked “sometimes” and provided a reason specific to cardiology knowledge, sometimes was

the final determination. If during investigator review, there was no consensus reached, a group meeting was held to reach consensus.

We present the reviewed individual medication substitutions in three categories: always acceptable, sometimes acceptable, and never acceptable with the following assumptions: (1) appropriate dosing adjustments can be made between medications for potency, half-life, and patient factors such as renal function; (2) patient can take the medication in the required form, for example if a PO medication replaces an IV medication; (3) medications are available on the US market; and (4) clinicians would review full medication lists for other DDIs prior to the substitution.

Finally, we present the 20 most frequent higher-order drug substitutions identified in previous work and deemed “always” accepted by this review of individual drug substitutions and the associated relative risks as calculated in previous work.¹⁰ Most frequent were defined as the substitutions in three- or four-drug combinations with significant *p* values that occurred with the highest frequency when Medicare fee-for-service and MarketScan Medicare supplement data were summed.

Results

Of the 286 dyads from previous work, 58 were removed on initial review as clearly not clinically acceptable by the initial two investigator review. Of the 228 remaining, after expert review, 84 dyads were categorized as always, 123 as sometimes, and 21 as never appropriate for substitution (Tables 1–3). There were no discrepancies remaining after final review by the two investigators considering specialty-specific knowledge, and, therefore, no consensus meeting was needed.

Of the 1904 high-risk combinations with lower-risk alternative combinations identified in our prior work,¹⁰ 606 had suggested drug substitutions that were deemed always acceptable; 588 were anticoagulant ADEs, 18 were opioid, and none were antidiabetic. The 20 most frequently observed high-risk combinations and the proposed substitutions are listed in Table 4; the top 20 all involved anticoagulant ADEs. Eleven of the top 20 involved suggested proton pump inhibitor substitutions, and 9 suggested statin substitutions. The complete list of high- and low-risk

Table 1. Individual drug substitutions are determined to be always acceptable and therefore clinically relevant among identified in three- and four-drug combinations with lower-risk substitutions.

Initial medication	Proposed substitute medication	Initial medication	Proposed substitute medication
Diazepam	Alprazolam	Enalapril	Lisinopril
Lorazepam	Alprazolam	Ramipril	Lisinopril
Nifedipine	Amlodipine	Alprazolam	Lorazepam
Rivaroxaban	Apixaban	Irbesartan	Losartan
Lovastatin	Atorvastatin	Olmesartan	Losartan
Pravastatin	Atorvastatin	Valsartan	Losartan
Rosuvastatin	Atorvastatin	Dexamethasone	Methylprednisolone
Simvastatin	Atorvastatin	Prednisolone	Methylprednisolone
Triamcinolone	Betamethasone	Prednisone	Methylprednisolone
Atenolol	Bisoprolol	Bisoprolol	Metoprolol
Metoprolol	Bisoprolol	Oxycodone	Morphine
Furosemide	Bumetanide	Amlodipine	Nifedipine
Torseamide	Bumetanide	Losartan	Olmesartan
Metolazone	Chlorthalidone	Valsartan	Olmesartan
Fluoxetine	Citalopram	Omeprazole	Pantoprazole
Sertraline	Citalopram	Citalopram	Paroxetine
Hydrocortisone	Dexamethasone	Escitalopram	Paroxetine
Methylprednisolone	Dexamethasone	Sertraline	Paroxetine
Omeprazole	Dexlansoprazole	Lovastatin	Pravastatin
Pantoprazole	Dexlansoprazole	Simvastatin	Pravastatin
Lisinopril	Enalapril	Enalapril	Quinapril
Citalopram	Escitalopram	Lisinopril	Quinapril
Sertraline	Escitalopram	Ramipril	Quinapril
Omeprazole	Esomeprazole	Enalapril	Ramipril
Pantoprazole	Esomeprazole	Lisinopril	Ramipril
Ranitidine	Famotidine	Atorvastatin	Rosuvastatin
Gemfibrozil	Fenofibrate	Citalopram	Sertraline
Dutasteride	Finasteride	Escitalopram	Sertraline
Citalopram	Fluoxetine	Atorvastatin	Simvastatin

(Continued)

Table 1. (Continued)

Initial medication	Proposed substitute medication	Initial medication	Proposed substitute medication
Escitalopram	Fluoxetine	Lovastatin	Simvastatin
Paroxetine	Fluoxetine	Pravastatin	Simvastatin
Sertraline	Fluoxetine	Rosuvastatin	Simvastatin
Budesonide	Fluticasone	Metformin	Sitagliptin
Salmeterol	Formoterol	Oxybutynin	Solifenacin
Glipizide	Glimepiride	Bumetanide	Torsemide
Glimepiride	Glipizide	Furosemide	Torsemide
Pioglitazone	Glipizide	Latanoprost	Travoprost
Tiotropium	Ipratropium	Losartan	Valsartan
Losartan	Irbesartan	Olmesartan	Valsartan
Valsartan	Irbesartan	Diltiazem	Verapamil
Omeprazole	Lansoprazole	Rivaroxaban	Warfarin
Bimatoprost	Latanoprost		
Sitagliptin	Linagliptin		

Table 2. Individual drug substitutions determined to be sometimes acceptable and therefore potentially clinically relevant among identified in three- and four-drug combinations with lower-risk substitutions.

Initial medication	Proposed substitute medication	Reviewer comment summary
Formoterol	Albuterol	Both can be used PRN, but formoterol must be used with an inhaled corticosteroid.
Colchicine	Allopurinol	In gout, it could be substituted, but colchicine is more often used for acute flares, and allopurinol more often as preventive. In inflammatory cardiac disease, it could NOT be substituted.
Warfarin	Apixaban	Warfarin is superior for LV thrombus and LVAD.
Quetiapine	Aripiprazole	Depends on the indication. For example, likely ok in depression but not for schizophrenia. Use caution in geriatric patients.
Risperidone	Aripiprazole	Different side effects to be considered.
Bisoprolol	Atenolol	Bisoprolol has mortality benefits over atenolol in CAD.
Metoprolol	Atenolol	Metoprolol XR has a mortality benefit in heart failure with reduced ejection fraction.

(Continued)

Table 2. (Continued)

Initial medication	Proposed substitute medication	Reviewer comment summary
Carvedilol	Atenolol	Carvedilol has mortality benefits over atenolol in CAD. Carvedilol also has alpha blockade and therefore has a greater blood pressure effect.
Budesonide	Betamethasone	Depends on the indication.
Methylprednisolone	Betamethasone	Betamethasone is not widely used intravenously.
Prednisone	Betamethasone	Depends on the indication. Ok for topical.
Timolol	Brimonidine	Different mechanisms of action.
Prednisone	Budesonide	Budesonide is more often used PRN, prednisone for a specific course.
Atenolol	Carvedilol	Atenolol has benefits in long QT syndrome that carvedilol does not.
Metoprolol	Carvedilol	Carvedilol has a more blood pressure effect. Metoprolol is favored for rate control in atrial fibrillation.
Timolol	Carvedilol	Carvedilol is not available for ophthalmic administration. Systemic carvedilol has more blood pressure effects than timolol.
Cephalexin	Cefdinir	Depends on the infection being treated.
Azithromycin	Cefuroxime	Depends on the infection being treated.
Levofloxacin	Ciprofloxacin	Depends on the infection being treated.
Azithromycin	Clindamycin	Depends on the infection being treated.
Timolol	Clonidine	Clonidine is not available for ophthalmic administration. Systemic clonidine has more blood pressure effects than timolol.
Nystatin	Clotrimazole	Depends on the infection being treated.
Hydrocodone	Codeine	Not often used interchangeably in clinical practice, but could consider if codeine is sufficient.
Allopurinol	Colchicine	Colchicine does not provide the same benefits as allopurinol for preventing crystal and tophi formation in gout. It would not be acceptable in tumor lysis syndrome or secondary prevention of renal stones.
Baclofen	Cyclobenzaprine	If on chronic baclofen, not acceptable. Baclofen has a benefit in hiccups, but cyclobenzaprine does not.

(Continued)

Table 2. (Continued)

Initial medication	Proposed substitute medication	Reviewer comment summary
Rivaroxaban	Dabigatran	Rivaroxaban is favored when body mass index >40.
Warfarin	Dabigatran	Warfarin is superior for LV thrombus and LVADs.
Sucralfate	Dexlansoprazole	If using for gastroesophageal reflux only and short term, possible. Sucralfate is used for short-term coating of the GI tract and is not sufficient alone for ongoing treatment of many pathologies.
Verapamil	Diltiazem	Verapamil has a greater effect on ventricular arrhythmias compared to diltiazem.
Memantine	Donepezil	Donepezil is approved for mild/moderate dementia. Memantine approved for severe dementia.
Metronidazole	Doxycycline	Depends on the infection being treated.
Bupropion	Duloxetine	Different drug classes.
Citalopram	Duloxetine	Different drug classes.
Mirtazapine	Duloxetine	Different drug classes.
Finasteride	Dutasteride	Appropriate for BPH. Finasteride has an indication for androgenic alopecia that dutasteride does not.
Atorvastatin	Fenofibrate	Atorvastatin has a mortality benefit in arterial disease compared to fenofibrate.
Ezetimibe	Fenofibrate	Ezetimibe lowers only cholesterol. Fenofibrate can lower triglycerides as well.
Tamsulosin	Finasteride	Dependent upon indication. For example, reasonable for BPH but not for nephrolithiasis.
Amiodarone	Flecainide	Flecainide is contraindicated in structural heart disease such as CAD, hypertrophic cardiomyopathy.
Nystatin	Fluconazole	Depends on the infection being treated.
Albuterol	Formoterol	Different half-lives may make it challenging to substitute.
Bumetanide	Furosemide	Furosemide may have lower bioavailability in patients with intestinal edema.
Torsemide	Furosemide	Furosemide may have lower bioavailability in patients with intestinal edema.
Levetiracetam	Gabapentin	Gabapentin does not have sufficient anti-epileptic activity for more than focal seizures.
Insulin	Glimepiride	Depends on insulin requirements and reason for insulin (e.g., not appropriate in DKA).

(Continued)

Table 2. (Continued)

Initial medication	Proposed substitute medication	Reviewer comment summary
Metformin	Glimepiride	Glimepiride has a higher risk of hypoglycemia.
Insulin	Glipizide	Depends on insulin requirements and reason for insulin (e.g., not appropriate in DKA).
Liraglutide	Glipizide	Liraglutide can cause weight loss. Glipizide causes weight gain and has an increased risk for hypoglycemia.
Metformin	Glipizide	Depends on whether the patient still makes insulin. Glipizide has an increased risk for hypoglycemia.
Codeine	Hydrocodone	Not often used interchangeably in clinical practice. Hydrocodone has a higher risk of sedation.
Betamethasone	Hydrocortisone	Acceptable topical substitution. Not acceptable for preterm labor.
Budesonide	Hydrocortisone	Acceptable topical substitution, but not other indications, such as respiratory.
Dexamethasone	Hydrocortisone	Acceptable for topical, but not for systemic.
Glimepiride	Insulin	It can be considered short term but may be inappropriate when less invasive medications are available.
Glipizide	Insulin	It can be considered short term but may be inappropriate when less invasive medications are available.
Liraglutide	Insulin	It can be considered short term but may be inappropriate when less invasive medications are available.
Metformin	Insulin	It can be considered short term but may be inappropriate when less invasive medications are available.
Diltiazem	Isosorbide	In general, it has different clinical indications. But it may be acceptable for blood pressure control.
Nitroglycerin	Isosorbide	In general, it has different clinical indications. But it may be acceptable for angina.
Fluconazole	Ketoconazole	Depends on the infection being treated.
Carvedilol	Labetalol	Carvedilol has mortality benefits over labetalol in CAD.
Timolol	Labetalol	Labetalol is not available for ophthalmic administration. Labetalol has both beta and alpha blockade effects.

(Continued)

Table 2. (Continued)

Initial medication	Proposed substitute medication	Reviewer comment summary
Polyethylene Glycol	Lactulose	Likely acceptable in cirrhosis. In other patients, lactulose causes more distension.
Famotidine	Lansoprazole	Acceptable for GERD. Not acceptable for antihistamine/allergic reaction.
Pantoprazole	Lansoprazole	Acceptable for GERD. It may not be acceptable in upper gastrointestinal bleeding.
Gabapentin	Levetiracetam	Both can treat focal seizures. Gabapentin treats neuropathic pain, and levetiracetam does not.
Ciprofloxacin	Levofloxacin	Depends on the infection being treated.
Amiodarone	Lidocaine	Consider sustained VT or VT storm due to ischemia. Not acceptable for atrial arrhythmias.
Atorvastatin	Lovastatin	Lovastatin cannot be used in place of high-dose atorvastatin.
Donepezil	Memantine	Donepezil is approved for mild/moderate dementia. Memantine approved for severe dementia.
Insulin	Metformin	Only if outpatient insulin requirements are compatible. Not for IV insulin indications such as DKA.
Sitagliptin	Metformin	Only if sufficient glucose control can be obtained with metformin.
Betamethasone	Methylprednisolone	Acceptable topical substitution. Not acceptable for preterm labor.
Hydrocortisone	Methylprednisolone	Acceptable for systemic use. Not acceptable for topical or mineralocorticoid effects.
Atenolol	Metoprolol	Atenolol has benefits in long QT syndrome that metoprolol does not.
Carvedilol	Metoprolol	Metoprolol has less blood pressure effect than carvedilol.
Timolol	Metoprolol	Metoprolol does not have an ophthalmic preparation.
Betamethasone	Mometasone	Not common clinically due to the primary modes of administration.
Budesonide	Mometasone	
Fluticasone	Mometasone	
Metronidazole	Nitrofurantoin	Depends on the infection being treated.
Isosorbide	Nitroglycerin	In general, it has different clinical indications. But it may be acceptable for angina.

(Continued)

Table 2. (Continued)

Initial medication	Proposed substitute medication	Reviewer comment summary
Famotidine	Omeprazole	Acceptable for GERD. Not acceptable for antihistamine/allergic reaction.
Pantoprazole	Omeprazole	Acceptable for GERD. It may not be acceptable in upper gastrointestinal bleeding.
Ranitidine	Omeprazole	Acceptable for GERD. It may not be acceptable in upper gastrointestinal bleeding. Note ranitidine is currently off the market.
Mirabegron	Oxybutynin	Acceptable for overactive bladder. Mirabegron also has an indication for detrusor overactivity.
Tramadol	Oxycodone	Different mechanism of action.
Atorvastatin	Pravastatin	Pravastatin cannot be used in place of high-dose atorvastatin.
Rosuvastatin	Pravastatin	Pravastatin cannot be used in place of high-dose rosuvastatin.
Betamethasone	Prednisolone	Acceptable topical substitution. Not acceptable for preterm labor.
Dexamethasone	Prednisolone	
Methylprednisolone	Prednisolone	
Prednisone	Prednisolone	
Betamethasone	Prednisone	Acceptable topical substitution. Not acceptable for preterm labor.
Dexamethasone	Prednisone	
Methylprednisolone	Prednisone	
Prednisolone	Prednisone	
Gabapentin	Pregabalin	Acceptable for most indications, but not in alcohol use disorder or herpetic neuralgia.
Risperidone	Prochlorperazine	Prochlorperazine has a higher risk of side effects.
Timolol	Propranolol	Propranolol is not available for ophthalmic administration.
Famotidine	Ranitidine	Ranitidine is currently off the market.
Pantoprazole	Ranitidine	Ranitidine is currently off the market.
Warfarin	Rivaroxaban	Warfarin is superior for LV thrombus and LVADs.
Donepezil	Rivastigmine	Primary clinical use differs; for example, donepezil is primarily used for dementia and rivastigmine for myasthenia gravis.

(Continued)

Table 2. (Continued)

Initial medication	Proposed substitute medication	Reviewer comment summary
Levodopa	Ropinirole	Levodopa is critical for Parkinson's disease and should not be routinely switched.
Pravastatin	Rosuvastatin	
Simvastatin	Rosuvastatin	
Albuterol	Salmeterol	
Formoterol	Salmeterol	
Finasteride	Tamsulosin	Appropriate for BPH. Finasteride has an indication for androgenic alopecia that dutasteride does not.
Terazosin	Tamsulosin	Appropriate for BPH. Terazosin has a role as adjunct therapy for hypertension that tamsulosin does not.
Zolpidem	Temazepam	Similar indications but different drug classes, and temazepam has a higher risk for dependence.
Finasteride	Terazosin	Terazosin may also affect blood pressure.
Tamsulosin	Terazosin	Terazosin may also affect blood pressure.
Atenolol	Timolol	Atenolol does not have an ophthalmic preparation.
Brimonidine	Timolol	If ophthalmologic, usually given together, but could be substituted in an appropriate patient. Brimonidine is not given systemically.
Carvedilol	Timolol	Carvedilol has mortality benefits over timolol in CAD.
Latanoprost	Timolol	If ophthalmologic, usually given together, but could be substituted in an appropriate patient. Not appropriate systemically.
Metoprolol	Timolol	Metoprolol has mortality benefits over timolol in CAD.
Ipratropium	Tiotropium	Ipratropium is more often used PRN; tiotropium is scheduled.
Mirtazapine	Trazodone	Reasonable for sleep indications. But mirtazapine is used for depression, and trazodone is not.
Hydrocortisone	Triamcinolone	Acceptable topical substitution.
Spirolactone	Triamterene	Acceptable for volume status, but spironolactone has a mortality benefit in CHF and is indicated in cirrhosis over triamterene.

BPH, benign prostatic hyperplasia; CAD, coronary artery disease; CHF, congestive heart failure; DKA, diabetic ketoacidosis; GERD, gastroesophageal reflux disease; LV, left ventricular; LVAD, left ventricular assist devices; PRN, pro re nata; VT, ventricular tachycardia.

Table 3. Individual drug substitutions are determined to be never acceptable and therefore clinically irrelevant among identified in three- and four-drug combinations with lower-risk substitutions.

Initial medication	Proposed substitute medication	Reviewer comment summary
Salmeterol	Albuterol	Salmeterol is scheduled. Albuterol is PRN. Should not be switched based on their role in asthma management.
Fenofibrate	Atorvastatin	Different clinical indication.
Sotalol	Carvedilol	Sotalol is used clinically as an antiarrhythmic and not as a beta blocker.
Metronidazole	Clotrimazole	Cover different organisms (fungal vs bacterial).
Isosorbide	Diltiazem	Different clinical indication.
Trazadone	Duloxetine	Different clinical indication.
Lidocaine	Flecainide	Different clinical indication.
Sotalol	Metoprolol	Sotalol is used clinically as an antiarrhythmic and not as a beta blocker.
Triamcinolone	Mometasone	
Diltiazem	Nitroglycerin	Different clinical indication.
Ezetimibe	Pravastatin	Different clinical indication.
Levetiracetam	Pregabalin	Different clinical indication.
Sotalol	Propranolol	Sotalol is used clinically as an antiarrhythmic and not as a beta blocker.
Ezetimibe	Rosuvastatin	Different clinical indication.
Fenofibrate	Rosuvastatin	Different clinical indication.
Atenolol	Sotalol	Sotalol is used clinically as an antiarrhythmic and not as a beta blocker.
Carvedilol	Sotalol	Sotalol is used clinically as an antiarrhythmic and not as a beta blocker.
Metoprolol	Sotalol	Sotalol is used clinically as an antiarrhythmic and not as a beta blocker.
Timolol	Sotalol	Sotalol is used clinically as an antiarrhythmic and not as a beta blocker.
Sotalol	Timolol	Sotalol is used clinically as an antiarrhythmic and not as a beta blocker.
Duloxetine	Trazodone	Different clinical indication.

combinations with always acceptable substitutions is provided in Supplemental Table 1. For example, for a patient taking furosemide, metoprolol, and pantoprazole, if pantoprazole is

replaced with dexlansoprazole, the associated relative risk of anticoagulant side effect is 0.689 in Medicare fee-for-service and 0.488 in MarketScan Medicare supplement data.

Table 4. The 20 most frequent high-risk three- and four-drug combinations and low-risk alternative drug combinations with high-risk drug combination and substitution that makes it a low-risk combination, as identified in previous work.¹⁰

Rank	Risk group	Drug 1	Drug 2	Drug 3	Drug 4	Medicare RR	MarketScan RR	Combined n																																																																																																																																																																																		
1	High	Furosemide	Metoprolol	Pantoprazole		0.689	0.488	1284																																																																																																																																																																																		
	Low			Dexlansoprazole					2	High	Atorvastatin	Clopidogrel	Pantoprazole		0.538	0.568	1219	Low			Dexlansoprazole		3	High	Clopidogrel	Metoprolol	Pantoprazole		0.716	0.745	1185	Low			Dexlansoprazole		4	High	Atorvastatin	Clopidogrel	Hydrochlorothiazide		0.881	0.856	1113	Low	Rosuvastatin				5	High	Furosemide	Levothyroxine	Simvastatin		0.977	0.886	1017	Low			Pravastatin		6	High	Furosemide	Levothyroxine	Pantoprazole		0.527	0.291	889	Low			Dexlansoprazole		7	High	Furosemide	Levothyroxine	Pantoprazole		0.770	0.739	889	Low			Esomeprazole		8	High	atorvastatin	Furosemide	Lisinopril	Metoprolol	0.821	0.741	788	Low	Rosuvastatin				9	High	Clopidogrel	Furosemide	Pantoprazole		0.546	0.412	753	Low			Dexlansoprazole		10	High	Allopurinol	Amlodipine	Atorvastatin		0.961	0.661	728	Low			Rosuvastatin		11	High	Furosemide	Omeprazole	Simvastatin		0.388	0.632	688	Low		Esomeprazole	Pravastatin		12	High	Atorvastatin	Carvedilol	Pantoprazole		0.32	0.429	688	Low			Dexlansoprazole		13	High	Clopidogrel	Lisinopril	Pantoprazole		0.734	0.74	661	Low			Esomeprazole		14	High	Clopidogrel	Levothyroxine	Pantoprazole		0.456	0.687	657	Low
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(Continued)

Table 4. (Continued)

Rank	Risk group	Drug 1	Drug 2	Drug 3	Drug 4	Medicare RR	MarketScan RR	Combined n
15	High	Albuterol	Atorvastatin	Furosemide		0.835	0.809	635
	Low		Rosuvastatin					
16	High	Furosemide	Lisinopril	Pantoprazole		0.696	0.682	623
	Low			Esomeprazole				
17	High	Atorvastatin	Clopidogrel	Levothyroxine	Metoprolol	0.815	0.844	571
	Low	Simvastatin						
18	High	Diltiazem	Levothyroxine	Metoprolol		0.754	0.762	570
	Low	Verapamil						
19	High	Carvedilol	Clopidogrel	Pantoprazole		0.635	0.806	564
	Low			Esomeprazole				
20	High	Atorvastatin	Carvedilol	Spironolactone		0.886	0.897	547
	Low	Rosuvastatin						

Relative risks are reported for Medicare fee-for-service and MarketScan Medicare supplement data separately. All top 20 are anticoagulant-induced adverse drug events.

In the Medicare fee-for-service data, there were 148,098 ED visits with a potential anticoagulant ADE. The 588 always acceptable high-/low-risk substitutions correspond to 46,665 ED visits. Therefore, 31.5% of the anticoagulant ADEs with a high-risk combination present had an acceptable low-risk alternative. Similarly, in MarketScan, this corresponded to 113,531 with ED visits with potential anticoagulant ADE, 50,087 with always acceptable substitution, and, therefore, 44.1% with a low-risk alternative.

In the Medicare fee-for-service data, there were 146,245 ED visits with a potential opioid ADE. The 18 always acceptable high-/low-risk substitutions correspond to 1048 ED visits. Therefore, 0.7% of the opioid ADEs with a high-risk combination present had an acceptable low-risk alternative. Similarly, in MarketScan, this corresponded to 116,781 ED visits with potential opioid ADE, 1441 with always acceptable substitution, and, therefore, 1.2% with a low-risk alternative.

There were no clinical substitutions for diabetic ADEs that were deemed always acceptable.

Discussion

We demonstrate that the findings of the mixture drug-count response model yield clinically relevant results. Almost one-third of the identified high-/low-risk substitutions were deemed always acceptable with appropriate assumptions. If applied to reduce the use of high-risk three- and four-drug combinations, these results could have immediate positive clinical impact on patients. Though not explicitly presented here, many more substitutions may be acceptable in certain scenarios.

We estimated that 31.5% and 44.1% of anticoagulant ADEs observed in the Medicare (2018) and MarketScan (2012–2020) datasets, respectively, had an acceptable lower-risk alternative regimen. This corresponds to 46,665 and 50,087 visits in the databases, respectively. Annually, this

is 46,665 and 5565. While this would be the upper bound of effect, substitution of a lower-risk alternative has the potential for large clinical significance of preventing tens of thousands of ADEs per year. Importantly, these lower-risk alternatives have equal therapeutic efficacy, are widely available, are highly familiar to prescribers, are generally inexpensive, and should be acceptable substitutions to the vast majority of prescribing physicians.

Similarly, we estimated that 0.7% and 1.2% of opioid ADEs observed in the Medicare and MarketScan datasets, respectively, had an acceptable lower-risk alternative regimen. This corresponds to approximately 1048 and 1441 visits in the databases, respectively. Annually, this is 1048 and 160. While this is a lower potential clinical impact than anticoagulation ADEs, this still has clear clinical applicability.

The primary limitation of this work is related to the use of large databases to identify the high- and low-risk drug combinations. There is no way to know if the potential ADEs were related to the medications or not. For example, a gastrointestinal bleed could occur as an ADE or due to the development of a bleeding ulcer that would have occurred with or without the high-risk medications. However, the relative risks are significant and imply that there is a real relationship. Furthermore, we do not know if the patients were taking the medications as prescribed.

Further work should seek to determine whether the high-risk combinations were felt to contribute to the side effect in real patient encounters, examine the identified high- and low-risk combinations to determine if there is an underlying pharmacologic explanation for the differences, and seek to change prescribing patterns to lower-risk combinations.

Conclusion

High-risk high-order DDIs with low-risk alternatives as identified in Medicare fee-for-service and MarketScan databases are clinically acceptable as determined by expert physician review of proposed substitutions. Substituting high-risk combinations for low-risk combinations could decrease ED visits resulting from anticoagulant

and opioid ADEs; in particular, substitutions of certain statins and PPIs could have the greatest effect.

Declarations

Ethics approval and consent to participate

This study was certified as non-human subjects research by The Ohio State University IRB. Accordingly, no consent to participate was necessary.

Consent for publication

Not applicable.

Author contributions

Katherine M. Hunold: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Project administration; Writing – original draft.

Yi Shi: Formal analysis; Writing – review & editing.

Pengyue Zhang: Formal analysis; Funding acquisition; Writing – review & editing.

Macarius M. Donneyong: Formal analysis; Funding acquisition; Writing – review & editing.

Alexander Ulintz: Data curation; Writing – review & editing.

Benjamin H. Buck: Data curation; Writing – review & editing.

Joshua I. Gordon: Data curation; Writing – review & editing.

Antoinette Pusateri: Data curation; Writing – review & editing.

Melanie Rayan: Data curation; Writing – review & editing.

Katherine Brownlowe: Data curation; Writing – review & editing.

Jeffrey M. Caterino: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The complete list of drug substitutions generated by the previous work is included as a Supplemental Material.

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Supplemental material

Supplemental material for this article is available online.

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