

Individualized Drug Interaction Alerts

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Structured Abstract

Purpose: The purpose of this project was to conduct a pilot health information technology research project focusing on the design of a novel drug-drug interaction knowledgebase and accompanying clinical decision support architecture to provide individualized DDI alerts. Our approach was to change the underlying framework for DDI alerting to an advanced and contextual CDS.

Scope: We examined drug-drug interactions (DDI) that are commonly ignored or overridden by healthcare providers to determine if computer algorithms could be more specific to patient characteristics and medication attributes.

Methods: The most frequently overridden DDI warnings from a large tertiary care medical center were obtained and those drug combinations where contextual factors may eliminate the need to warn of potential harm were studied. Data were extracted from electronic health records and the DDI algorithms were applied to determine the frequency of alerting using the current approach and new algorithms.

Results: A total of 21 combinations were evaluated, with 12 having characteristics amendable for developing CDS alert algorithms. These characteristics included patient attributes (age; renal function; pharmacogenomic status; prior medical history; laboratory measurements) and drug attributes (dose; duration of therapy; formulation; route of administration; and concomitant therapy). The reduction in the number of alerts ranged from zero to 100% depending on the drug pair. The study suggests that DDI alerting algorithms can be developed to reduce irrelevant warnings associated with DDIs.

Key Words:

clinical decision support, alerts, drug interactions, medication safety, CPOE

REPORT

1. Purpose

Healthcare providers have succinctly summarized that, “**The current drug-drug interaction (DDI) alert system is broken.**”^{1,2} Electronic prescribing and pharmacy systems include alerts for DDIs as a form of clinical decision support (CDS) to warn prescribers and pharmacists of potentially harmful medication combinations, and ideally provide documentation on how to avoid or mitigate the risk of patient harm. However, the promise of improved outcomes remains unfulfilled because there is an excessive volume of alerts perceived by clinicians as irrelevant or unhelpful; over 90% of DDI alerts are overridden.^{3,4}

Proprietary drug knowledgebases (KBs) were not initially envisioned to support DDI checking, but rather as pricing and inventory systems.⁵ Current systems are ineffective, particularly among institutions or practices lacking sufficient resources to customize commercially available products. Given these issues, the specific aims of this project were:

- 1) Prototype a rules-based DDI KB with attributes necessary for patient-specific and contextual alerting;**
- 2) Develop clinical algorithms that extract and use data from an existing commercially available EHR system and integrates with the DDI KB; and**
- 3) Conduct a validation of clinical algorithms using simulated and actual patient data.**

2. Scope

Background

Clinicians override approximately 90% or more of DDI alerts, primarily because the alerts are not considered relevant.^{3,4,6} Excessive irrelevant alerts are thought to decrease users’ sensitivity to alerts, producing what is known as the *cry-wolf phenomenon*, *alarm fatigue*, or more specifically *alert fatigue*.^{3,7,8} Alert fatigue is more than just a frustration; it can lead clinicians to respond inappropriately.⁹

Electronic prescribing and pharmacy systems include alerts for DDIs as a form of clinical decision support (CDS) to warn prescribers and pharmacists of potentially harmful medication combinations, and ideally provide documentation on how to avoid or mitigate the risk of patient harm. However, this technology has fallen short of fulfilling its potential to improve patient safety. It is urgent that these issues be addressed because more and more healthcare organizations in the United States are trying to include DDI alerts in their plans to achieve meaningful use of electronic health records (EHRs) (i.e., CMS Meaningful Use Core Measure 2).^{10,11}

Approaches to reduce alert fatigue include turning-off entire categories of alerts or using expert opinion to refine commercial KBs to a smaller set of DDIs, and tiering alerts by relative potential clinical importance.^{3,4,10,12,13} However, most institutions lack the resources and expertise to customize off-the-shelf KBs.² Furthermore, patient specificity plays a major role in alert acceptance.^{3,14-16} In one study, when alerts failed to provide contextual information, prescribers bypassed the alert and then searched for the relevant data they needed.¹⁷ There are many situations where a particular DDI alert might not be clinically relevant to a specific patient due to mitigating factors that result in a negligible risk of adverse outcomes. For example, angiotensin-converting enzyme (ACE) inhibitors and potassium-sparing diuretics are frequently used together with good therapeutic results among patients with adequate kidney function and normal potassium levels. Adjudication of DDI seriousness should be based on an assessment of contextual factors such as the patient’s age, dosing regimen, duration of therapy, route of administration, timing sequence, concomitant medications, and predisposing diseases.^{15,18-20} Therefore, to reduce excessive and irrelevant alerts, DDI alerts must be filtered and prioritized by contextual factors that increase or decrease risk of a harmful interaction.

Limited research has been conducted regarding intelligent filtering and context-based DDI alerts. Duke *et al.* designed a model to integrate patient-specific data into DDI alerts via a web-based service that was interoperable across clinical information systems.²¹ In a randomized controlled follow-up study, Duke *et al.* found no improvement in prescriber adherence to DDI alerts that included the patient’s most recent relevant laboratory values for hyperkalemia-associated DDIs among high-risk patients.²² It is important to note that Duke *et al.*’s alerting system did not use patient-specific information to intelligently filter alerts for clinicians.

Rather, the alerts simply showed the relevant laboratory values, assuming clinicians would make the necessary cognitive connections. The authors acknowledged that stating the elevated risk for each patient might have improved adherence. This study suggested the importance of addressing alert specificity. For example, alerts for lower-risk patients could have been filtered or downgraded. Such tiering, or prioritizing, of alerts has been shown to improve adherence.¹⁰

Studies have demonstrated the potential for substantial reductions in alert volume when rules engines incorporate contextual factors. Riedmann *et al.* used a combination of literature searches and expert interviews to design a context model of 20 factors that could be used to prioritize drug safety alerts depending on the characteristics of the specific patient (e.g., clinical status), alert (e.g., severity), and user or organizational unit (e.g., professional experience of user).²³ Seidling *et al.* observed that more than half of the alerts that would have been triggered for DDIs involving cholesterol-lowering statin drugs were inappropriate because the dose of the statin was not considered by the software.²⁴ More recently, Seidling *et al.* identified 14 types of modulators useful for refining the specificity of DDI alerts.¹⁵ These could be applied to 83 out of 100 frequently triggered DDI alerts using relevant factors in the EHR. However, the clinical relevance of this work was limited by the fact that the investigators did not conduct an evaluation of the altered alerts to determine appropriateness. In preliminary work, researchers in the Netherlands observed up to an 80% reduction in alerts to prescribers following modifications to alerting rules.²⁵ Horn *et al.* were able to reduce the potential number of major alerts by nearly 70% by applying an operational classification that specified DDI clinical management strategies to a commercial KB.¹³ However, more research is needed to evaluate the effect of implementation of contextual factors in DDI alerting systems.

This project was designed to support **the next generation** of DDI CDS rules and data necessary that fulfill the five rights of CDS as outlined by AHRQ (getting the right information to the right stakeholder, at the right point in workflow, through the right channel, and the right format).²⁶ One of the most important of these is the first – the right information. The project was a pilot health IT research project focusing on the design of a novel DDI alert approach. Major contributions from this pilot project will be 1) generation of patient-specific modifiers and drug specific attributes that can be used to influence if a DDI alert is provided to a prescriber or pharmacist; and 2) determine the feasibility of clinical algorithms to reduce alert burden. Results from this study can inform future projects and research to broaden the development of drug and patient specific DDI alerting to increase the specificity of DDI warnings.

Context: To meet the requirements of meaningful CDS as specified by the Office of the National Coordinator for Health Information Technology, organizations must include DDI checking. Thus, nearly all hospitals and most clinics and physician offices have implemented electronic health records (EHRs) that include DDI warnings.

Settings: The setting for this study was two-fold. One setting was the University of Arizona Medical Center (UAMC), a 385-bed flagship hospital of the University of Arizona Health Network. UAMC-South is a sister facility that primarily serves medically indigent and underserved minority populations residing in south Tucson. Together, patient care units cover the range of clinical services including pediatrics, surgery including transplantation, oncology, medical and cardiac intensive and non-intensive care units, obstetrics and gynecology, neurology, and mental health. Algorithm validation was conducted using data obtained from these facilities.

The second source of data for this study was from a simulated population of Medicare beneficiaries developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI), a multi-stakeholder, interdisciplinary collaborative to bring the value of observational health data through large scale analytics. This group is developing and promoting a common data model called OMOP. The validation of clinical algorithms using a common data model allows for greater update and distribution of project algorithms. In addition, we placed the developed algorithms on OHDSI's GitHub repository as part of the open-source software that researchers and others can access for research and other projects.

Participants: A sample of patients admitted to both UAMC facilities were selected over a 3-month time period based on having received 1 or more medications of interest. From this cohort we identified those observations exposed to drug combinations of interest. A total of 50 patient profiles was randomly selected to evaluate each drug combination of interest. Observations were excluded if they are: 1) observation only visits (non-admitted);

2) patients seen only in the emergency department; and 3) procedural based visits. Participants needed to be 18 years of age or greater to be included in the profile review. For each subject of interest data was queried from the EHR databases, excluding name, medical record number, and any other data that would identify a patient. Data from laboratory tests and results (including dates/times), medication orders (including medication name, strength, dose, route, frequency, start and stop date/time, and directions for administration), physiological parameters (including date and time of measurement), patient demographics including age in years, and diagnosis codes were used to construct patient profiles.

3. Methods

The research team met on a weekly schedule for the first year of the project and then approximately bi-weekly. Each meeting was conducted using Go-To-Meeting. Each meeting was organized as follows: roll call, review of agenda items, discussion of agenda items, action items to be completed before next call, and scheduling of next call. Prior to the next meeting, meeting minutes and upcoming meeting was emailed to the study team. A cloud-based storage folder was created and shared as a central location for sharing files.

Specific Aim 1: Prototype a rules-based DDI KB with attributes necessary for patient-specific and contextual alerting.

The research team met for 1-hour webinars on July 24th, July 31st, August 7th, August 14th, August 21st, August 28, September 10th, September 28th, October 2nd, October 9th, October 23rd, October 30th, November 13th, November 20th, and December 11th 2015, January 4th, and January 15th 2016 with primary discussion regarding the most commonly overridden drug pairs based upon a 90-day period at Banner - University Medical Center. The first priority was to determine which drug-drug interactions were most frequently overridden. Using a warnings report, we were able to generate a summary of the most commonly overridden drug pairs. Due to the pilot nature of this study, only those combinations of “serious” drug-drug combinations were investigated further. This list of drug combinations was then examined more closely to identify those pairs that have patient or drug specific factors associated with their use that would modify the risk of harm. Because warnings were often grouped by pharmacological/therapeutic class as well as individual chemical entities within a class, each drug-drug combination was evaluated.

For each drug combination, we searched the primary literature and used the extensive holdings of articles amassed by Drs. Hansten and Horn over the course of 40 years to identify potential factors. Search terms used in abstracting databases included the products (names) involved in the interaction as well as therapy specific terms associated with the combination. This included general pharmacology class and outcomes associated with exposure to the combination. We also searched using the term “interaction,” “drug-drug interaction,” “drug interaction,” or combination of both object and precipitant medication names. From articles of interest we evaluated citations for additional studies. Other sources included product labeling via NLM’s DailyMed²⁷ or FDA’s preapproval reviews and other documents via Drugs@FDA²⁸; DrugBank,²⁹ and medication reference databases subscribed to by the University of Arizona College of Pharmacy (Facts & Comparisons, Micromedex, Lexi-Comp Online, and the United States Pharmacopeial Convention National Formulary (USP-NF)).

Specific Aim 2: Develop clinical algorithms that extract and use data from an existing commercially available EHR system and integrates with the DDI KB.

The grant team met for 1-hour webinars on January 27th, February 11th, February 24th, March 7th, March 24th, April 12th, April 26th, May 11th, June 1st, July 7th, July 21st, August 4th, August 10th, August 25th, September 2nd, September 22nd, October 12th, October 21st, October 27th, November 9th, December 12th, and December 21st 2016, January 13th, and January 23rd 2017.

For each of the drug combinations, evidence was assembled to identify risk factors that would increase or decrease the risk of harm. Depending on the number of issues associated with each interaction, a decision table was constructed to represent factors and characteristics that would affect the risk of harm. Within each decision table were recommendations for 1) no special precautions; 2) assess risk and take action if necessary; and 3) use only if the benefit outweighed the risk.

After decision tables were constructed, clinical algorithms were then developed using standard ontologies. Medications of interest were mapped to the National Library of Medicine’s RxNORM concept

unique identifier (CUI). Algorithms then restricted the products of interest to those used for human consumption. Restrictions based on formulations were then applied. Clinical algorithms took into account factors affecting risk of harm and included: dose over 24-hour period; formulation; duration of therapy; route of administration; and concomitant therapy, including products that may inhibit or induce drug metabolism. Patient factors were identified and linked to LOINC codes for laboratory tests and International Classification of Disease 9th or 10th Edition – Clinical Modification for conditions and past medical history affecting risk. We also considered factors such as site of care (inpatient versus ambulatory). Pharmacoeconomic information was also considered when developing the algorithms, but due to the lack of a standard ontology we did not specify particular genomic procedures or results from those procedures.

Both written protocols and schematic flow diagrams were developed to represent the clinical algorithms. In addition, clinical algorithms were written using Drools software language, a platform by the Open Source CDS platform (OpenCDS). Drools is a Java-based open source business management system.

Specific Aim 3: Conduct a validation of clinical algorithms using simulated and actual patient data.

The grant team met for 1-hour webinars on February 10th, February 17th, March 1st, March 7th, March 22nd, April 3rd, April 11th, April 19th, April 26th, May 3rd, May 8th, May 16th, May 24th, May 30th, June 8th, June 22nd, and June 29th. Since the end of funding, the investigators have continued to meet to work on publications and analyses. Meetings have been held on July 10th, July 19th, August 8th, and August 23rd.

As mentioned above, two separate data sources were used to test and validate the clinical algorithms, including Banner University Medical Center – Tucson, and a simulated population of Medicare beneficiaries developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI). The simulated Medicare dataset was used to ensure that the clinical algorithms would run against a common data model. Only 1,000 persons are included in the dataset and not all data elements necessary for each algorithm was available. Thus, we added additional variables to the simulated data to ensure that all algorithms would execute without errors.

The data from the Banner University Medical Center Tucson was used to determine the reduction in alerts by comparing the number of alerts generated without the clinical algorithms as compared to the number of alerts generated using the clinical algorithms. A sample of patients from UAMC facilities was randomly selected over a 3-month time period based on having 1 or more DDI “serious” alerts identified in Aim 1. A total of 50 (see sample size calculation below) stays (defined as an admission and discharge) were randomly selected to evaluate each drug combination of interest. Observations of interest included persons 18 years of age or older.

Data from each observation was extracted from an EHR and included laboratory tests and results (including dates/times), medication orders (including medication name, strength, dose, route, frequency, start and stop date/time, and directions for administration), physiological parameters (including date and time of measurement), patient demographics including age in years, and diagnosis codes.

To facilitate the evaluation of the DDI algorithms the patient profiles were loaded into Microsoft Access and a “dashboard” layout was created. Information was grouped by type of data. For example, laboratory tests and results were located in one area of the dashboard, prescribed medicines in another. This facilitated record reviews.

For each DDI combination of interest, the summary data were reviewed by a physician/pharmacist and a pharmacist and applying the logic from the DDI algorithms developed in aim 2. The primary outcome for each observation was the classification of alert (i.e., upgrade, downgrade, and data not available). To ensure consistency across reviewers, the evaluation was conducted by the physician/pharmacist and then reviewed by a pharmacist. Discrepancies between the two reviewers was discussed to determine if algorithms need modification to fine-tune the criteria or if it is unfeasible to use a patient centric algorithm for that particular DDI. This information was then shared with the entire research team to discuss modifications of the algorithms. The algorithms were then discussed with respect to the feasibility of the algorithm and barriers or potential issues that would limit the application of the algorithm.

For the subset of patients that were manually reviewed the frequency of outcomes for the DDI algorithms was determined. The positive predictive validity for each potential DDI was calculated where true positives were identified by the two clinical reviewers as the patient being at risk for harm from the DDI. The

rate of false positives (defined as an alert being generated when not necessary) to true positive and total alerts was calculated. Due to the pilot nature of this study we were not able to determine the true negative rate because it would require a more time consuming complete medical chart review.

4. Results

Aim 1: Prototype a rules-based DDI KB with attributes necessary for patient-specific and contextual alerting.

Data on the frequency of DDI warnings that were overridden are shown in Table 1. Due to the pilot nature of this study, it was determined to examine only those interactions where the frequency of overrides over a 3-month period exceeded 1,000 times. For example, the most common combination that was presented was for fentanyl or opioid products with select medications that inhibit the cytochrome P450 3A4 pathway. Nearly 5,000 alerts were presented to clinicians over a 3-month period for this combination.

Object and Precipitant Medications	Overrides
Alfentanil; Fentanyl; Hydrocodone; Oxycodone / SLT 3A4 Inhibit	4835
Anticoagulants / Salicylates	2842
Varicella - Live Vaccines / Live Vaccines	2568
Potassium Preps / Potassium Sparing Diuretics	2545
Hepatitis B - Selected Live Viral Vaccines / Selected Immunoglobulins	2490
Selected Immunosuppressants / Azole Antifungal Agents	2306
Citalopram / QT Prolonging Agents	1892
Amiodarone / Possible QT Prolonging Agents	1739
Ketorolac / Anticoagulants	1603
MMR - Live Vaccines / Live Vaccines	1576
Clonidine / Beta-Blockers	1476
Selected Anticoagulants / SSRIS; SNRIS	1473
MMR - Selected Live Viral Vaccines / Selected Immunoglobulins	1472
Anticoagulants / Thyroid	1426
Intravenous Ceftriaxone / Intravenous Calcium Products	1387
Metoclopramide / Antipsychotics; Phenothiazines; Rivastigmine	1358
Quetiapine / QT Prolonging Agents	1131
Epinephrine / Beta-Blockers	1095
Trazodone / QT Prolonging Agents	1070

These “serious” DDIs were further evaluated to determine if patient or medication characteristics could affect the risk of harm such that an alert could be suppressed when no harm was likely. For those potential DDI combinations involving medication classes (i.e., azole agents, potassium-sparing diuretics, select 3A4 inhibitors, QT prolonging agents, beta-blockers, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, antipsychotics, anticoagulants), each unique combination of object and precipitant medications were reviewed to assess the potential for a DDI, not just a theoretical interaction. This further narrowed the specific medications to be included in the clinical algorithms (Aim 2). The investigators identified those combinations to further develop alerting algorithms and are shown in Table 2.

Potential Drug-Drug Interaction	Total Warnings Overridden
Opioids / Fluconazole	4835
Warfarin / Salicylates	2842
Potassium supplement / Potassium-sparing Diuretics	2545
Immunosuppressants / Azole Antifungals	2306
Amiodarone / QT Prolonging Agents	1739
Clonidine / Beta-Blockers	1476
Warfarin / SSRIs; SNRIs	1473
Ceftriaxone / Calcium	1387
Metoclopramide / Antipsychotics	1358
Epinephrine / Beta-Blockers	1095
Warfarin (a subset of all anticoagulants) / NSAIDs	342
Citalopram / QT Prolonging Agents	1892

Evaluation of these medications and their attributes was conducted using several drug databases including the World Health Organization's (WHO) anatomical therapeutic classification system, MicroMedex, Facts and Comparisons, and Lexi-Comp. For example, non-steroidal anti-inflammatory drugs (NSAIDs) are classified by the WHO into 9 specific subclasses as shown in Table 3 below. Given that each specific product could be linked to multiple therapeutic classes and that new formulations, strengths, combinations, routes of administration, and derivatives are constantly being developed and marketed, we decided that it would not be efficient to construct an entirely new drug knowledgebase but rather focus our efforts on developing clinical algorithms using the RxNORM database developed and maintained by the National Library of Medicine and other standard ontologies. This would more likely result in the clinical algorithms being more widely adopted and avoid the need to continually update the database to accommodate additions/removals for specific drug products (at the national drug code level).

Therapeutic Class Code	Description
N02AJ08	Opioids in combination with non-opioid analgesics: codeine and ibuprofen
M01AE14	Propionic acid derivatives: dexibuprofen
C01EB16	Other cardiac preparations
G02CC01	Anti-inflammatory products for vaginal administration
M01AE01	Propionic acid derivatives: ibuprofen
M02AA13	Anti-inflammatory preparations, non-steroids for topical use
R02AX02	Other throat preparations: ibuprofen
M01AE51	Propionic acid derivatives: ibuprofen combinations
N02AJ19	Opioids in combination with non-opioid analgesics: oxycodone and ibuprofen

Decision tables were constructed for the 12 combinations of interest. Figure 1 below is an illustrative example for the decision table involving beta-blockers and epinephrine.

Figure 1: Decision Table for Beta-Blockers and Epinephrine

Beta-Adrenergic Blockers + Epinephrine													
Epinephrine given in the presence of beta-blockade											Beta blocker given after epinephrine		
Order of administration	Inhaled	Ophthalmic Epinephrine	Epinephrine combined with local anesthetic ¹	Injection Resulting in Systemic Epinephrine Effects									
Epinephrine route of administration													
Normal use													
Dermatologic use													
Plastic surgery use													
Epinephrine indication													
Beta-blocker													
Route of administration													
Dose > 100 mg/d ²													
16 (CI) < 40 mg/d ³													
Dose > 20 mg/d ⁴													
Dose > 300 mg/kg ⁵													
Is patient CYP2D6 PM ⁶ ?													
Patient taking a CYP2D6 inhibitor ⁷													
Dose > 10 mg/d ⁸													
Dose > 20/d ⁹													
Acute hypertensive reaction ¹⁰													
Acute hypertensive reaction may occur, but benefit may outweigh risk ¹¹													
Acute hypertensive reaction is likely ¹²													
Acute hypertensive reaction is possible ¹³													
<p>Legend: ○ = No special precautions. ■ = Assess risk and take action if necessary. ◆ = Use only if benefit outweighs risk</p>													
<p>Footnotes:</p> <ol style="list-style-type: none"> Inhaled or ophthalmic epinephrine can sometimes produce systemic effects, but it does not seem likely that it would result in a significant hypertensive reaction. Epinephrine is often combined with local anesthetics to prolong the effect of the anesthetic. The amount used in routine dental procedures or in dermatologic practice (e.g., Moh's surgery) is unlikely to produce a hypertensive reaction with beta-blockers. Hypertensive reactions have been reported in patients receiving local anesthetics plus epinephrine for facial plastic surgery (for such use, go to first line of decision table and follow "Injection for Systemic Effects"). In most other cases where epinephrine is used with local anesthetic, the amount of epinephrine absorbed systemically would not be sufficient to produce a hypertensive reaction. But if large amounts are used (such as with facial plastic surgery) acute hypertension may occur. In patients on beta-blockers who are actually in anaphylaxis, administration of epinephrine tends to have very little (positive or negative) effects. So most agree that epinephrine should be given to treat anaphylaxis, but one should also be ready to use alternative measures (fluids, etc.). If epinephrine is used to prevent anaphylaxis in a beta-blocker treated patient who has been exposed to a potentially anaphylaxis-producing event (e.g., a wasp sting), it is recommended to give the epinephrine as usual. Since the patient is not yet in anaphylaxis, a hypertensive reaction may occur, but the potential benefit of the epinephrine almost certainly outweighs the risk of the acute hypertensive reaction. When a systemic dose of epinephrine is given to a person on one of these nonselective beta-blockers, an acute hypertensive reaction is almost certain. Systolic BPs of 250 mmHg are not uncommon. Most people can probably withstand a short episode of such a hypertensive reaction without permanent sequelae, but strokes have occurred in susceptible patients. Thus, it is best to avoid this reaction if possible. If a patient is likely to receive systemic epinephrine, it would be prudent to use a cardioselective beta-blocker. Timolol is a nonselective beta-blocker, but systemic absorption of epinephrine from the eye gel appears to be minimal compared to the drops. Thus a hypertensive reaction is unlikely. With timolol eye drops, however, many cases of systemic beta-blockade have been reported, so a hypertensive reaction is possible. At doses over 100 mg/day, atenolol can result in nonselective beta-blockade. Atenolol and bisoprolol undergo renal elimination, and may produce nonselective beta-blockade with significant renal impairment. At doses of 20 mg/day or higher, bisoprolol can result in nonselective beta-blockade. At doses over 300 mg/kg/min, esmolol can result in nonselective beta-blockade. At doses over 100 mg/day, metoprolol can result in nonselective beta-blockade. Metoprolol is metabolized by CYP2D6, and patients who are deficient in CYP2D6 (PMs) may develop higher metoprolol plasma concentrations and nonselective beta-blockade. Metoprolol is metabolized by CYP2D6, and patients who are receiving moderate to potent CYP2D6 inhibitors may develop higher metoprolol plasma concentrations and nonselective beta-blockade. Moderate to potent CYP2D6 inhibitors include: abiraterone, amiodarone, bupropion, diphenhydramine, duloxetine, fluoxetine, paroxetine, etc., etc. At doses over 10 mg/day, nebivolol can result in nonselective beta-blockade. Nebivolol is metabolized by CYP2D6, and patients who are deficient in CYP2D6 (PMs) may develop higher nebivolol plasma concentrations and nonselective beta-blockade. Nebivolol is metabolized by CYP2D6, and patients who are receiving moderate to potent CYP2D6 inhibitors may develop higher nebivolol plasma concentrations and nonselective beta-blockade. Moderate to potent CYP2D6 inhibitors include: abiraterone, amiodarone, bupropion, diphenhydramine, duloxetine, fluoxetine, paroxetine, etc., etc. Large doses of betaxolol may result in nonselective beta-blockade. Data suggests that doses about 20mg / day there is some loss of selectivity. Carvedilol and labetalol are nonselective beta-blockers but they both have some alpha-blocking effects. Theoretically a systemic dose of epinephrine would be less likely to produce a hypertensive reaction with these two drugs than with other nonselective beta-blockers. Systemic doses of epinephrine normally act for only a short time (minutes) so if a beta-blocker is given after the epinephrine, no interaction would be expected. 													

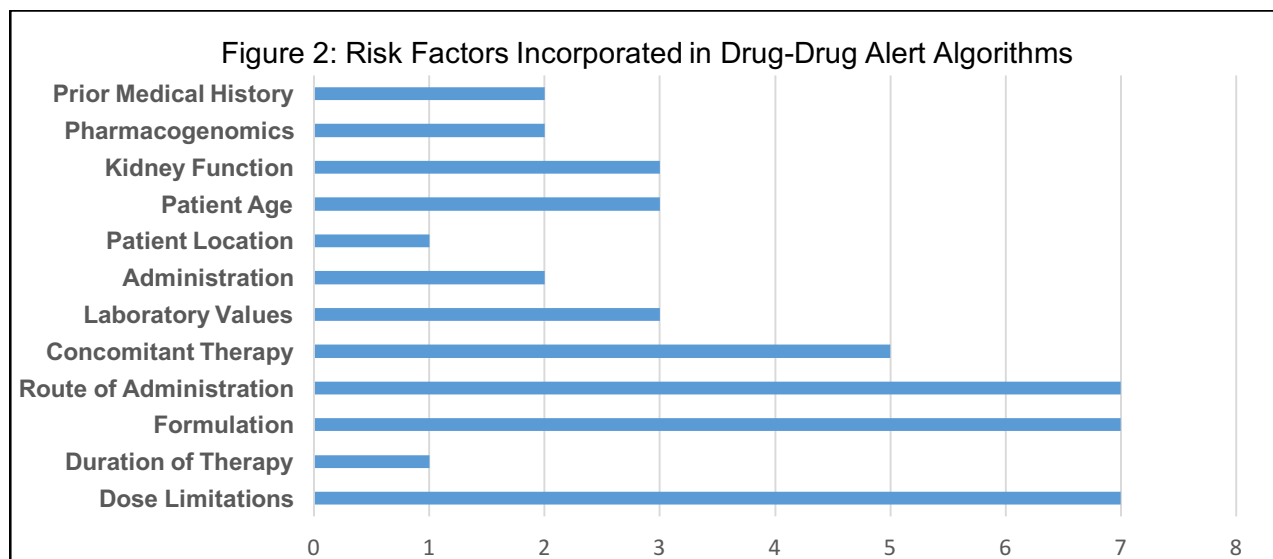
Specific Aim 2: Develop clinical algorithms that extract and use data from an existing commercially available EHR system and integrates with the DDI KB.

Decision tables and corresponding alerting algorithms were developed to address alert fatigue associated with potential DDIs for the 12 pairs shown in Table 2. The investigators met via conference call to discuss the decision table developed in Aim 1 as it was transformed into an alerting algorithm. For each combination, we searched RxNorm for the drug specific RxCUI values. For diagnoses and relevant past medical history, we evaluated ICD-9-CM and ICD-10-CM codes.

Algorithms developed over the course of the project are shown in the Appendix. Numerous factors were considered when developing the algorithms, as illustrated in the alerting algorithm for beta-blockers and epinephrine. This particular algorithm takes into account route of administration for both epinephrine and beta-blockers, intended use of the epinephrine, and type attributes of the beta-blocker with respect to cardiac selectivity, dose, patient renal function, and concomitant medications.

As another example, the alert algorithm for potassium supplements and potassium-sparing was limited to potassium-sparing diuretics to only three products, spironolactone, amiloride, and triamterene. Some drug compendia include other diuretics but there was no evidence to support their inclusion in this alert. The algorithm includes factors such as dose of both products, patient age, presence and value of serum potassium laboratory test, and kidney function. The warfarin and salicylates interaction algorithm starts with the route of administration for the salicylates is the first decision point in the algorithm, with no warnings needed for topical administration. For systemic administration of salicylates, non-acetylated and aspirin are treated separately. For non-acetylated products, dose of 3 grams per day requires a warning. For aspirin, doses greater than 100mg/day are of concern. The alerting algorithm for immunosuppressants is specific to only fluconazole. All other azole anti-fungal agents require an alert to be given due to their inhibition of cytochrome P-450 enzymes. For fluconazole, the route of administration and subsequent dose influences the need for alerts, with oral dosages greater than 100mg/day or intravenous doses greater than 200mg/day being problematic.

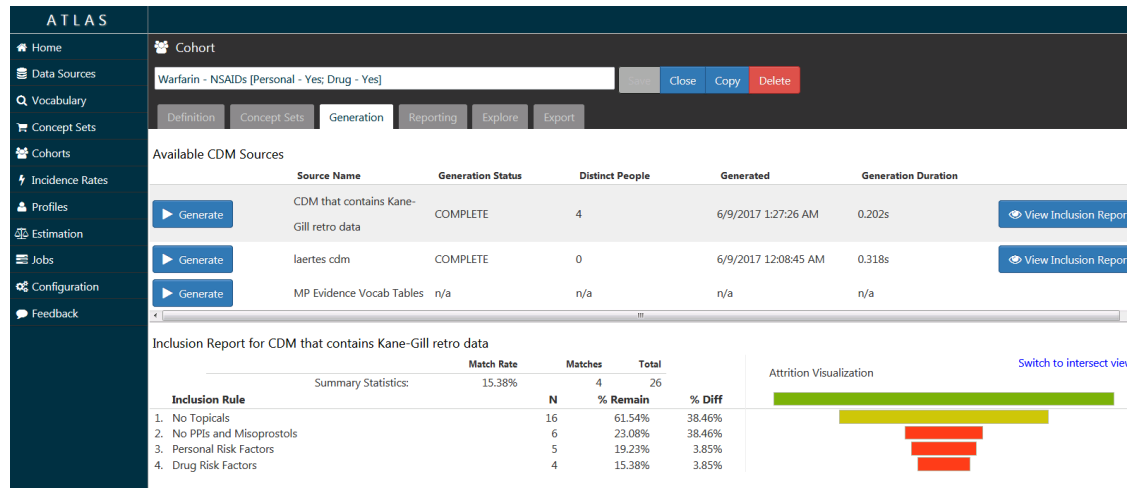
Figure 2 shows the frequency that both drug and patient risk factors were incorporated into alerting algorithms. For drug characteristics, the most frequent factors were dose, route of administration and formulation. Lower doses are not likely to result in an interaction that can cause harm. Also, topical and other non-systemic routes of administration were not likely to result in a DDI as well. Among the 12 algorithms, kidney function and patient age were the most common patient-specific characteristics that were incorporated.



Each algorithm was programmed in JBoss Drools rules to permit implementation within a common data model environment. All of the algorithms have been placed on the GitHub.com website. The algorithms and related concept sets can be found at: https://github.com/dbmi-pitt/iDIA_Rules. A Docker version of the entire stack of rules is available at: <https://github.com/dbmi-pitt/docker-iDIA-Rules>.

Once the Drools algorithms were developed, they were tested against the Medicare simulated dataset. Figure 3 below displays the application of the algorithm for warfarin and NSAIDs with respect to the proportion of subjects having these criteria.

Figure 3: Results from Drug-Drug Interaction Alerting Algorithm for Warfarin and NSAIDs



The algorithms were then applied to EHR data from Banner University Medical Center Tucson and South facilities over a 3-month period from January 1, 2016 to March 31, 2016. Table 5 displays the demographic characteristics of persons who were eligible to be included in the patient profiles. For each drug combination, individuals taking both medications were eligible to be randomly sampled for inclusion in the profile review. As demonstrated below, vulnerable populations were eligible for inclusion in the analysis. Thirty-eight percent of the cohort was of Hispanic or Latino ethnicity and nearly 23% were non-White/Caucasian. The average age was 50 years with a maximum age of 105.

Attribute	N	Percentage
Total	23712	100%
Race		
American Indian / Alaska Native	1011	4.3%
Asian/ Pacific Islander / Hawaiian	308	1.3%
Black	1179	5.0%
Multi-racial	198	0.8%
Other	2249	9.5%
White or Caucasian	18342	77.3%
Refused / Unknown	425	1.8%
Missing	11	-
Ethnic Group		
Hispanic or Latino	9012	38.0%
Not Hispanic or Latino	14269	60.2%
Refused	54	0.2%
Unknown	374	1.6%
Missing	14	
Sex		
Females	13009	54.8%
Males	10713	45.2%
Unknown	1	0.0%
	Mean	Standard Deviation
Age	50.1	19.5
Min = 18, Max = 105		

Each algorithm was evaluated against a random sample of admissions. Table 6 displays the results from applying the algorithms to patient profiles involving drug combinations with modifiable risk factors. This analysis assumed that an alert is necessary when the combination should be used only if the benefit outweighs the risk or if the provider (physician or other prescriber) needs to assess the risk and take action if necessary.

Drug Pair	Number of Profiles	Alerts Simple Algorithm	Alerts Complex Algorithm	PPV for Simple Algorithm (%)	Improvement in PPV (%)
Amiodarone / QT prolonging agents	50	150	8	5.3%	94.7%
Citalopram / QT prolonging agents	50	93	0	0.0%	100.0%
Clonidine/beta-blockers	50	84	4	4.8%	95.2%
Epinephrine / beta-blockers	50	50	1	2.0%	98.0%
Immunosuppressants / Fluconazole	46	342	114	33.3%	66.7%
Opioids / Fluconazole	50	169	13	7.7%	92.3%
Potassium / potassium-sparing diuretics	39	127	50	39.4%	60.6%
Warfarin / Non-steroidal anti-inflammatory drugs	49	67	66	98.5%	1.5%
Warfarin / salicylates	52	199	26	13.1%	86.9%
Warfarin / selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors	50	122	67	54.9%	45.1%

The results from the patient profile reviews illustrates that for many of the combinations the implementation of the alerting algorithms would lead to a substantial reduction in the number of warnings without placing patients at harm from a DDI. The improvement in positive predictive value (PPV) ranged from 1.5% to 100%, with greater than 45% improvement in PPV occurring in all but one situation. For the warfarin/NSAIDs combination, there was only a reduction of 1 alert with the complex algorithm, attributable to the absence of gastrointestinal medications that would reduce the risk of bleeding.

It is important to note that for warnings related to metoclopramide and antipsychotics there were no modifying factors. Also, for interactions involving QT prolonging medications, there was a lack of evidence to permit significant modifications.

5. Discussion

The results from this project suggest that significant improvements in warnings for DDIs is possible by incorporating drug- or patient-specific attributes. As discussed earlier, current drug knowledgebases are designed to alert on the presence of the medications, not taking into account factors that would mitigate the risk. This leads to excessive alerts. Our research suggests that many commonly overridden alerts can be suppressed using existing EHRs data. In many instances, it was challenging to identify appropriate decision points, especially for renal function and potassium levels. Therefore, we used conventional values but more research is needed to ensure the appropriate value is incorporated into the algorithms. In general, more research on the harms associated with DDIs is needed.

There are a number of limitations that should be kept in mind when interpreting the results of this pilot study. The patient profiles generated for this analysis required patients to be receiving both object and precipitant medications, but data on the number of alerts was not available directly. We estimated the number of alerts that would be generated by new orders taking into account start date/time and end date/time. For some patients, they were not taking products concurrently so no alert would be generated. This may have biased the number of simple alerts downward. The patient profiles were not admission specific, meaning that data for patients with multiple admissions during the observation period was included in the analysis.

Conclusions

This study demonstrates that algorithms can be successfully designed to reduce alert burden associated with DDIs. Up to 100% improvement in PPV may result if drug and patient factors are taken into consideration when evaluating co-administration of medications.

Significance

The findings from this project suggest that alert fatigue associated with DDIs may be partially addressed by implementing drug and patient specific alerting algorithms. This may lead to fewer clinically relevant DDI warnings being overridden, thereby reducing exposure to potentially harmful combinations.

Implications

This pilot project evaluated the feasibility of creating a DDI knowledgebase and associated alerting algorithms. While the creation of a DDI-specific knowledgebase for medications is challenging, creating and implementing algorithms for specific drug combinations is feasible. Future studies are needed to study the implementation of such algorithms to ensure patient safety is not compromised.

List of Publications and Products

There are no publications for this project at this time.

Algorithms for the DDIs of interest have been written in Drools and can be found on GitHub at: https://github.com/dbmi-pitt/iDIA_Rules. Furthermore, a docker container with all rules is available at: <https://github.com/dbmi-pitt/docker-iDIA-Rules>.

Priority Populations

Subjects of all demographic backgrounds were eligible for inclusion in this study. The data used for this study was obtained from persons who were admitted to Banner University Medical Center Tucson and South inpatient facilities. Because observations were randomly selected for evaluation, inclusion of persons from vulnerable groups, including minority racial/ethnic populations, are represented in the study. This includes

older persons because they are more likely to be on the medications of interest. Furthermore, females were included in the study. Due to the nature of the project, pediatric populations were not included in the analysis. Because this project uses retrospective data, there are no outreach activities applicable to the study.

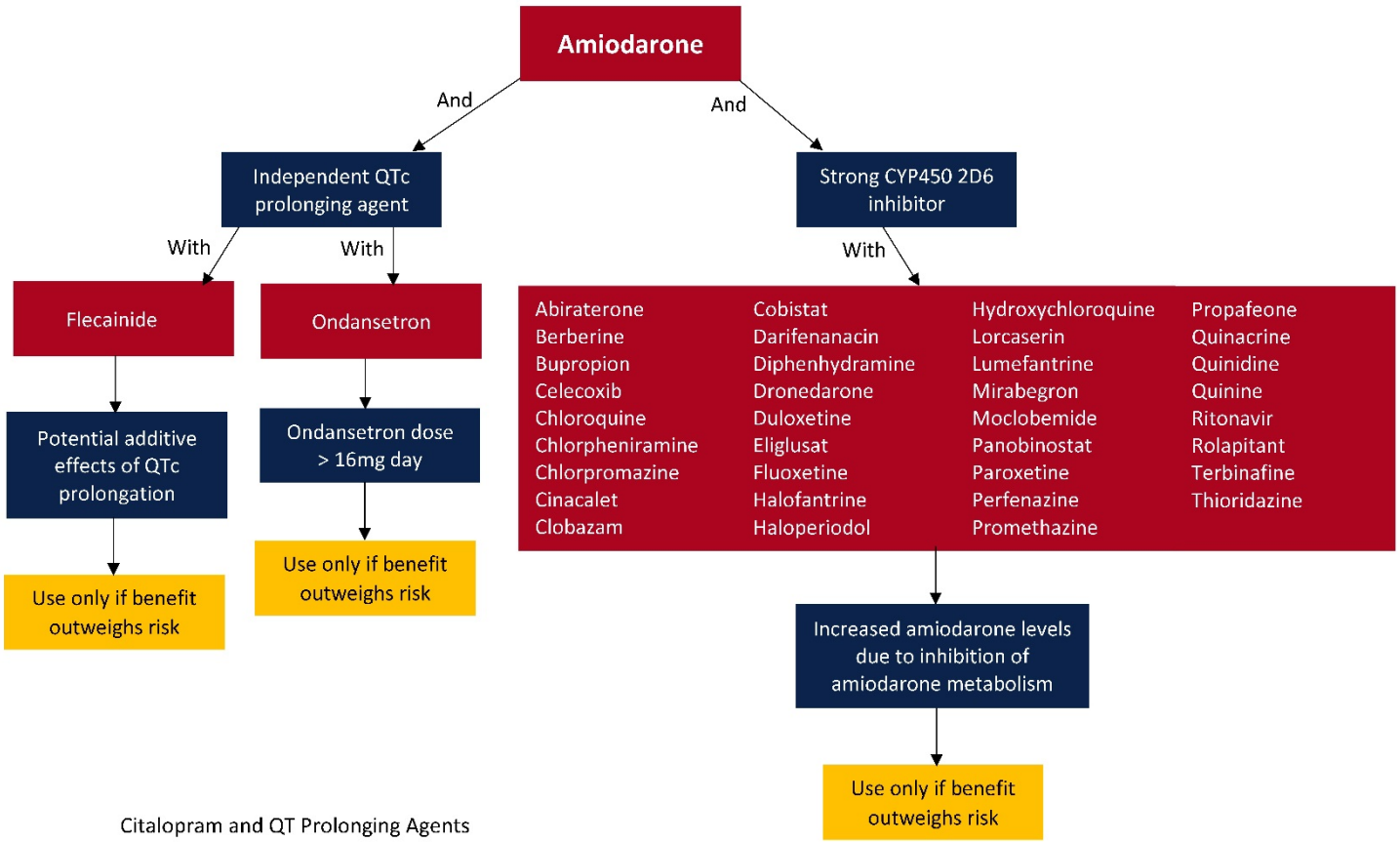
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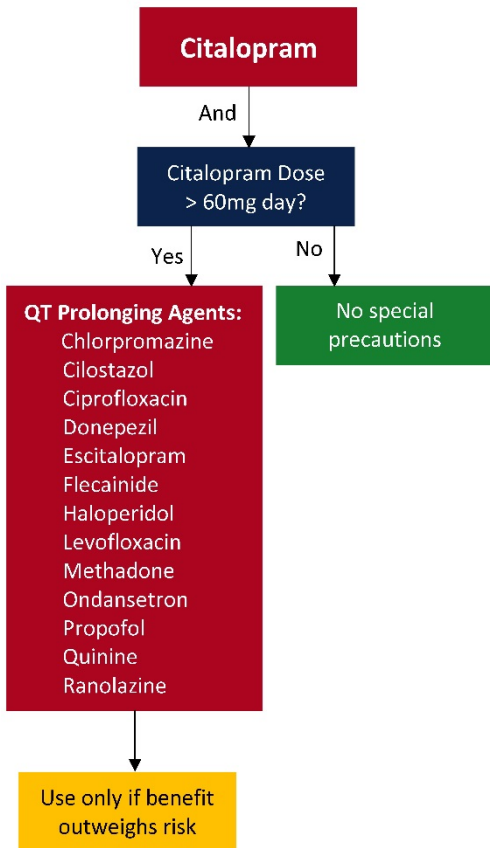
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Appendix

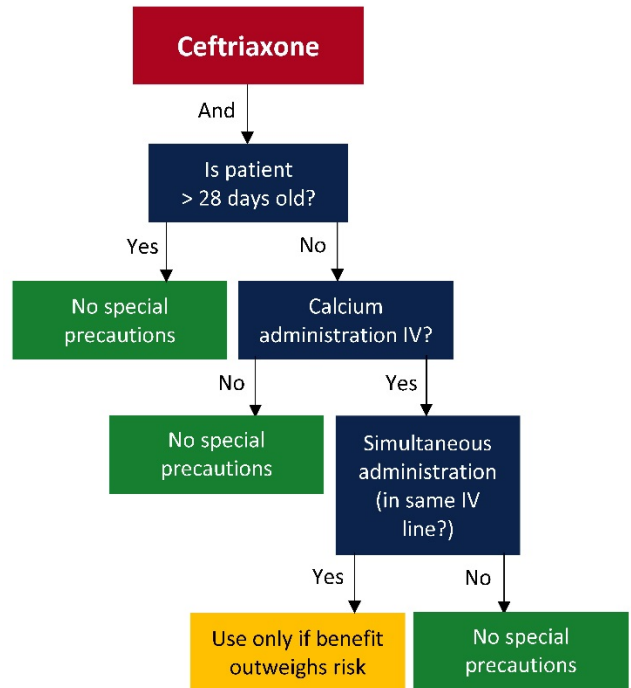
Amiodarone and QT Prolonging Agents



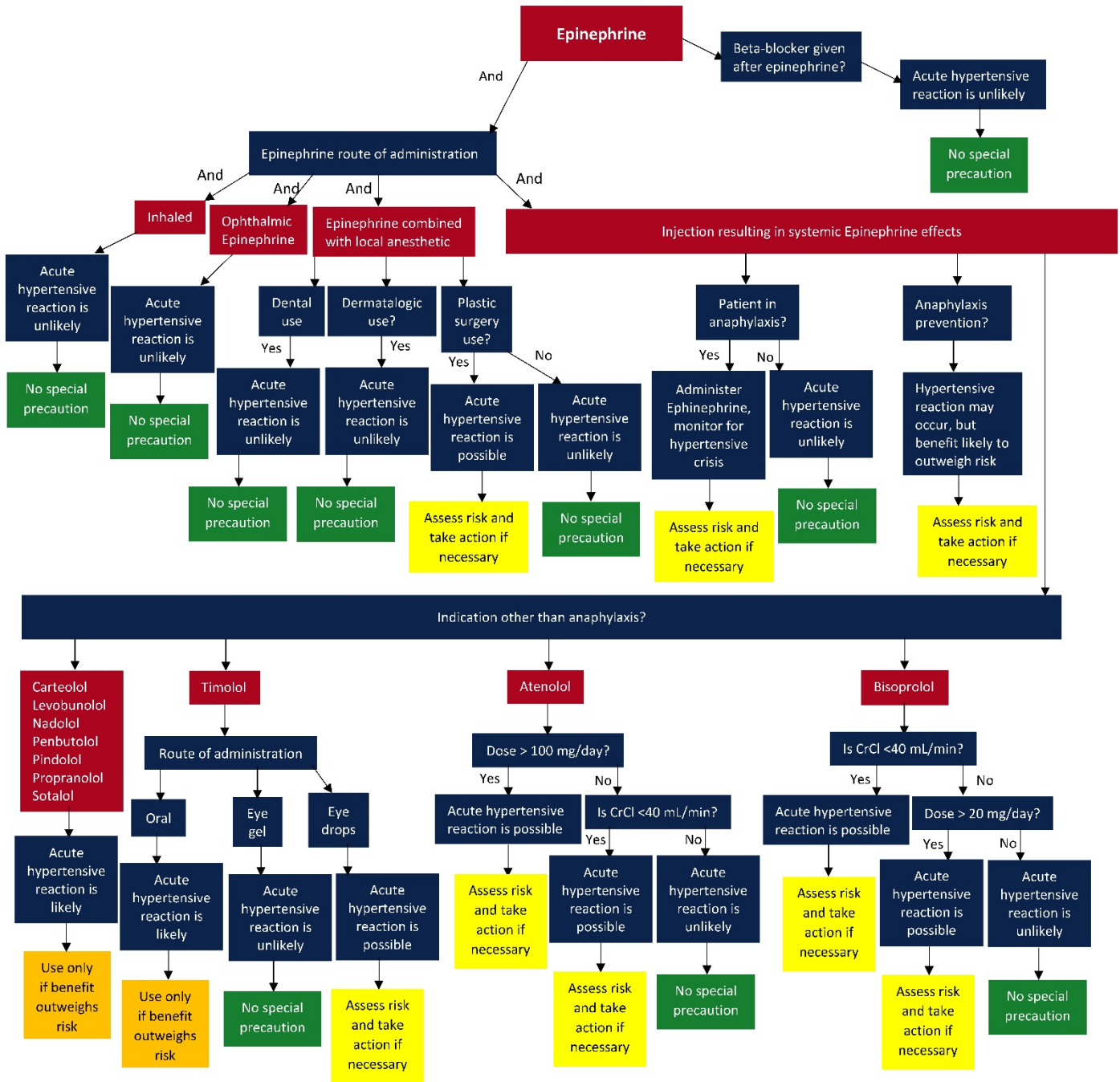
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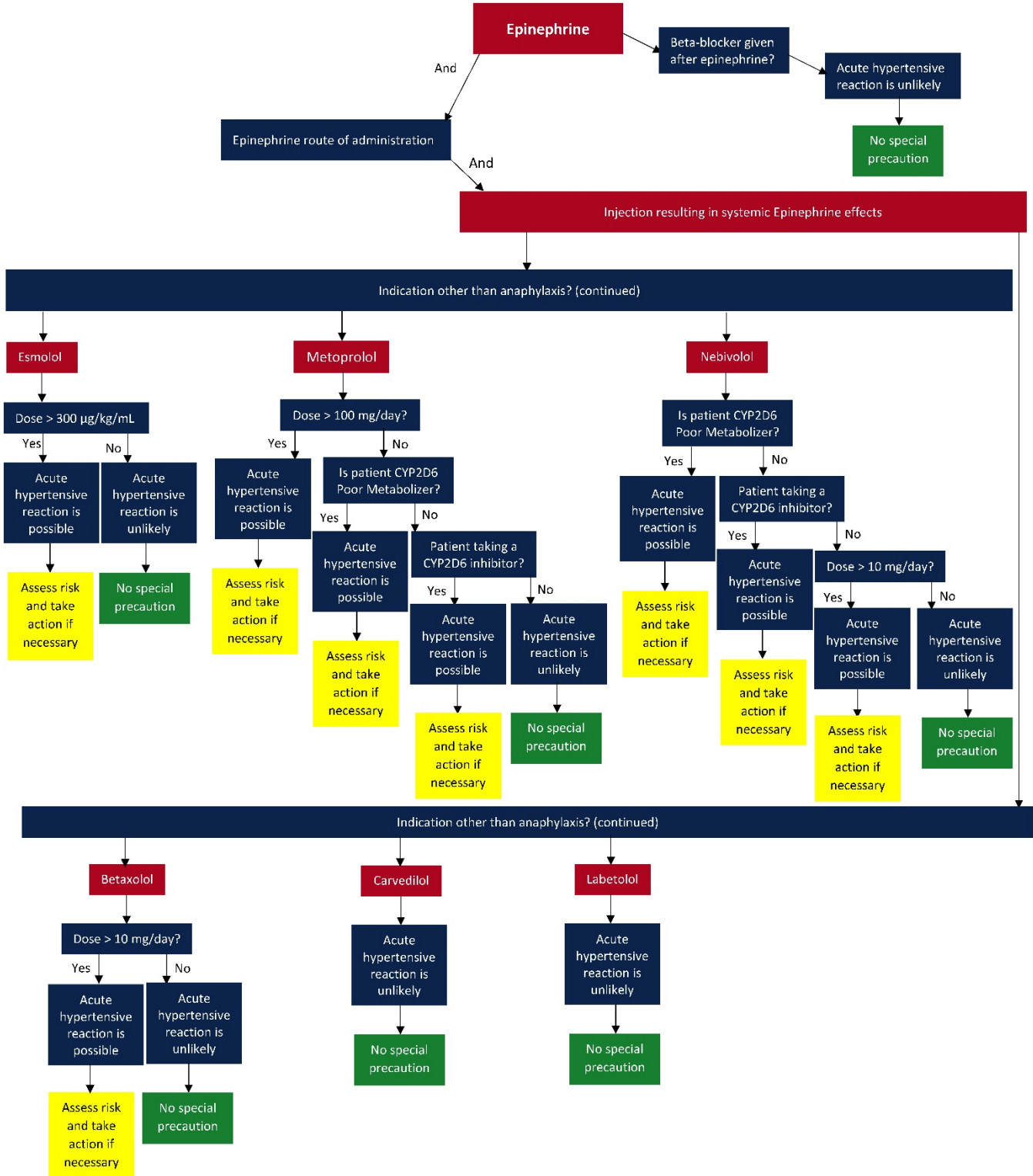
Ceftriaxone and Calcium



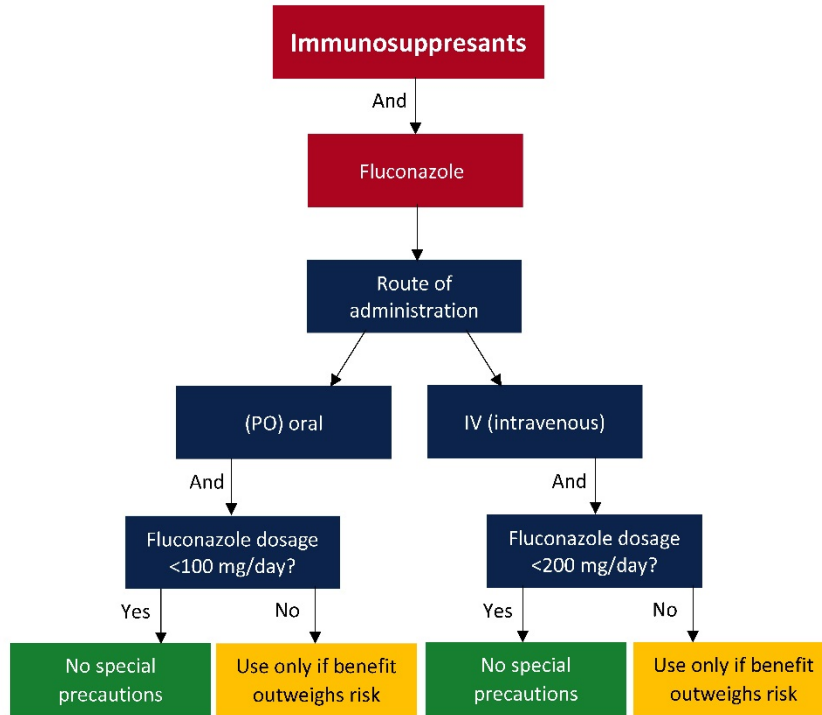
Beta-Adrenergic Blockers and Epinephrine



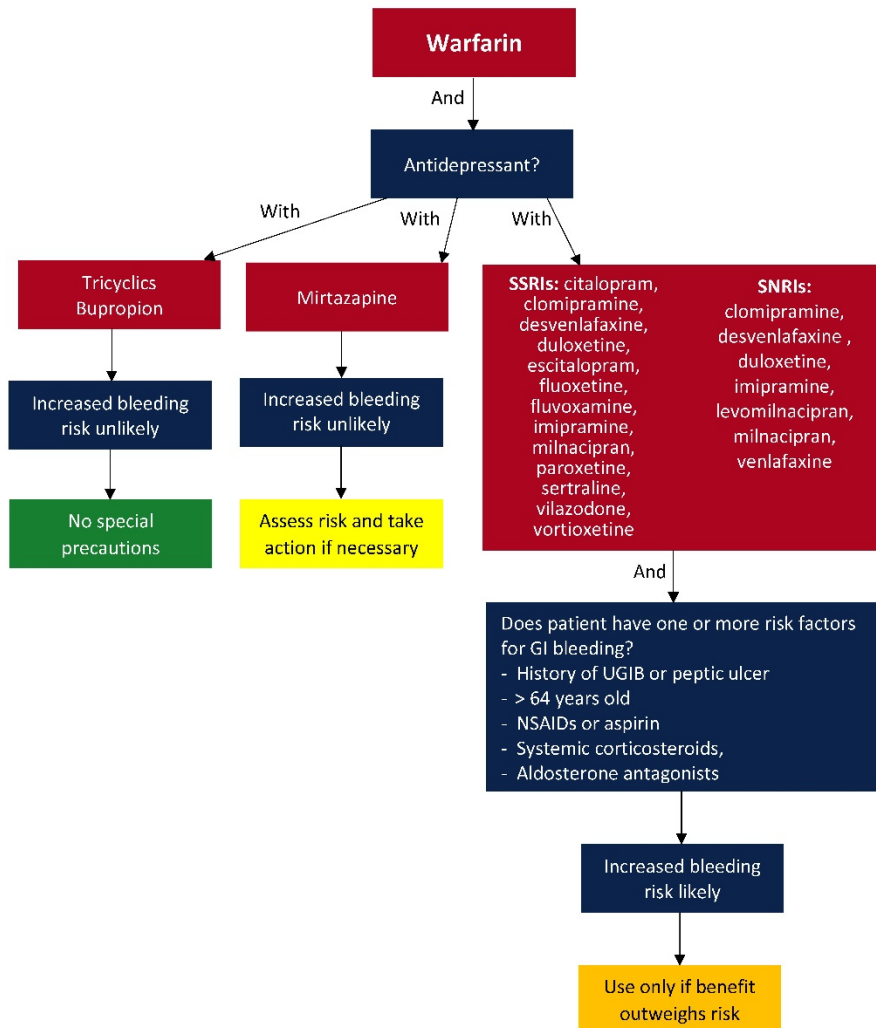
Beta-Adrenergic Blockers and Epinephrine



Immunosuppressants and Fluconazole

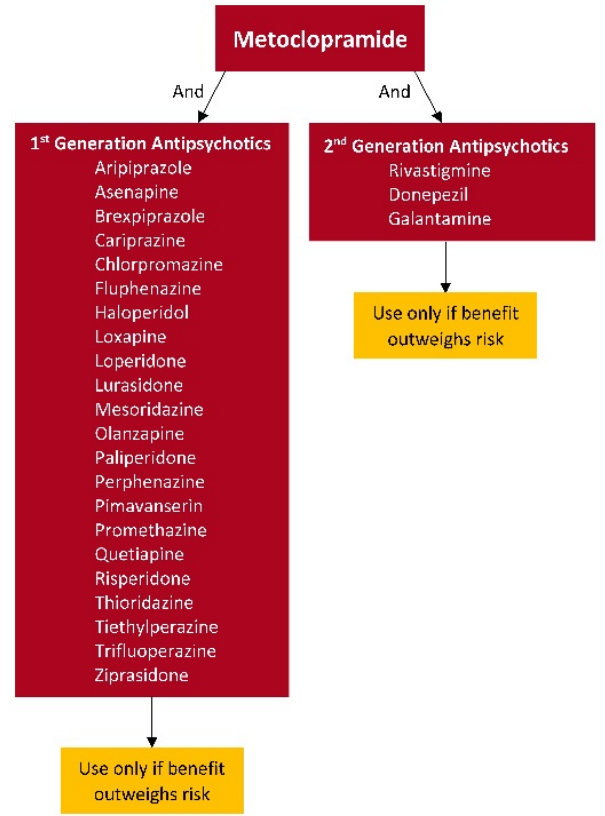
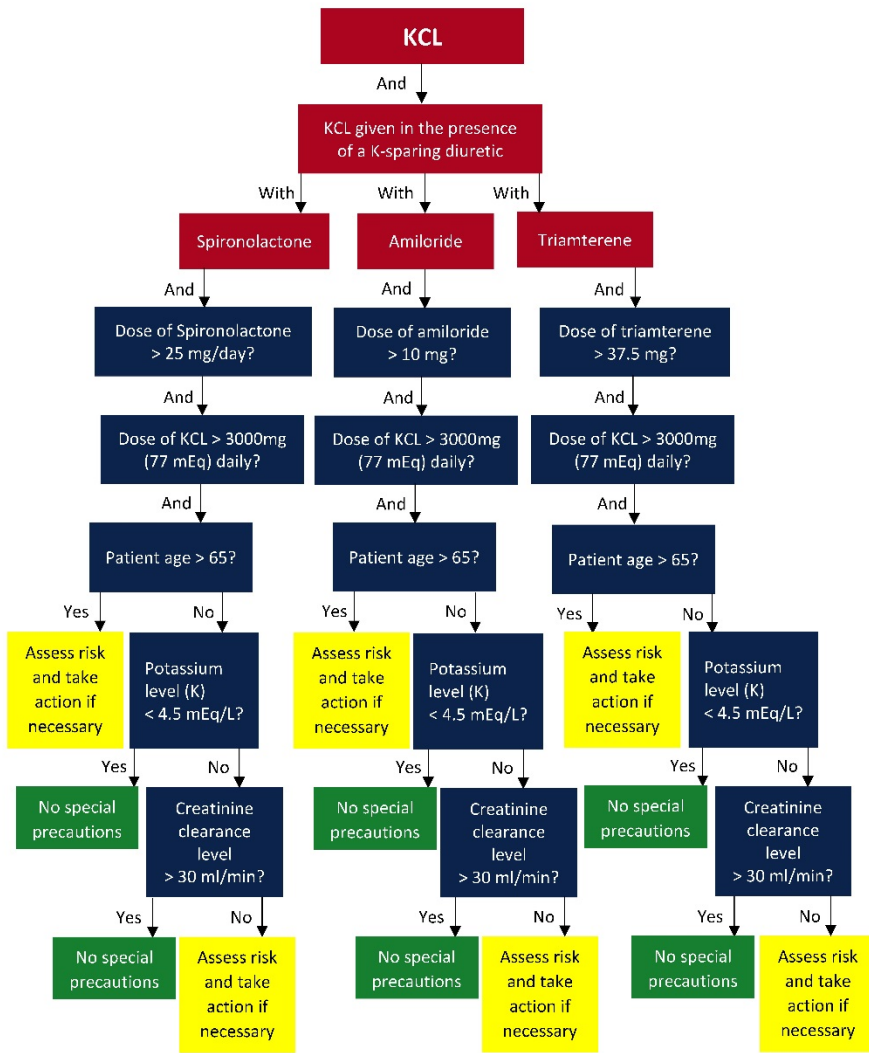


Warfarin and SSRIs

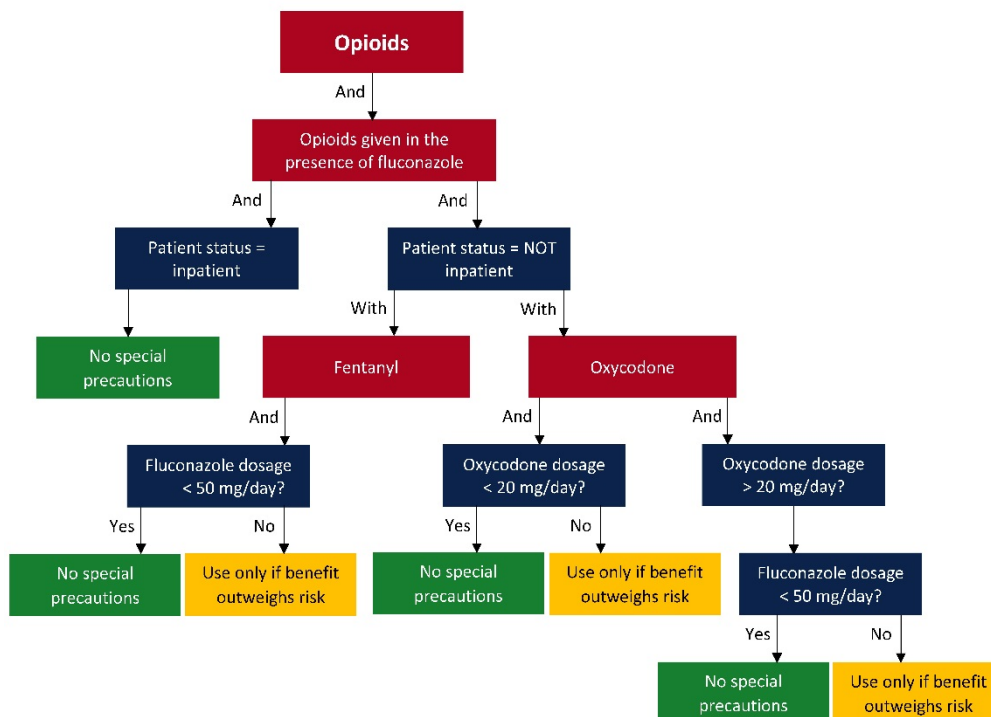


KCL and K-Sparing Diuretics

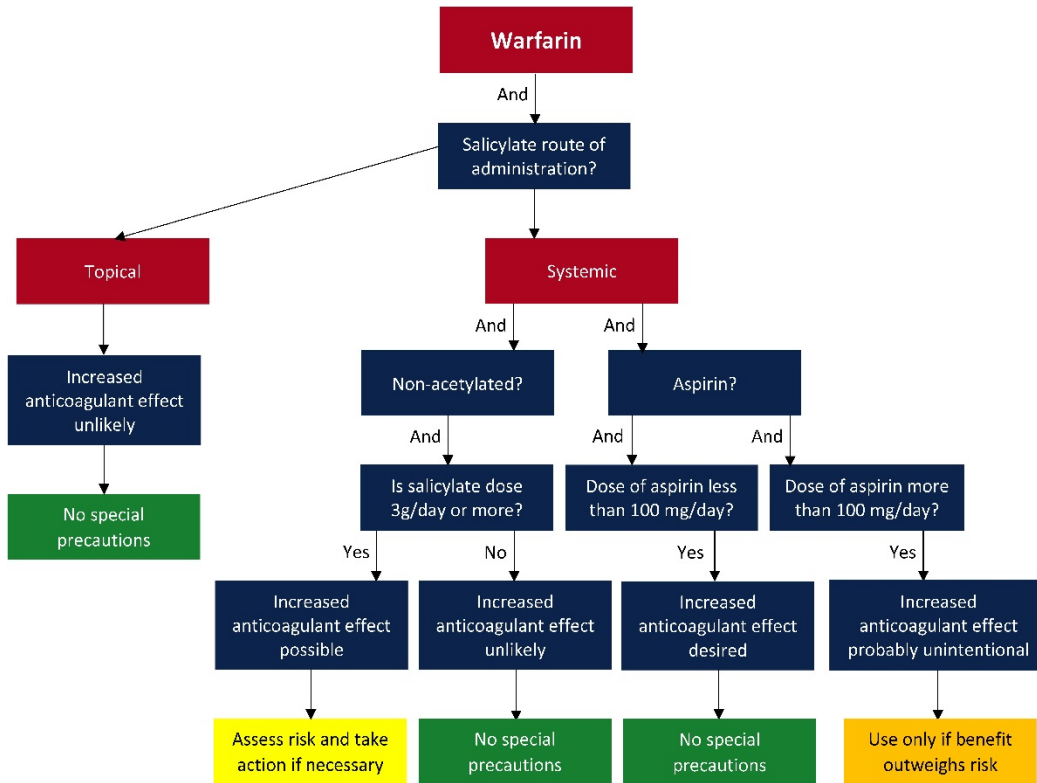
Metoclopramide and Antipsychotics Rivastigmine



Opioids and Fluconazole



Warfarin and Salicylates



Warfarin and NSAIDs

