High-priority drug—drug interactions for use in electronic health records

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ABSTRACT

Objective To develop a set of high-severity, clinically significant drug—drug interactions (DDIs) for use in electronic health records (EHRs).

Methods A panel of experts was convened with the goal of identifying critical DDIs that should be used for generating medication-related decision support alerts in all EHRs. Panelists included medication knowledge base vendors, EHR vendors, in-house knowledge base developers from academic medical centers, and both federal and private agencies involved in the regulation of medication use. Candidate DDIs were assessed by the panel based on the consequence of the interaction, severity levels assigned to them across various medication knowledge bases, availability of therapeutic alternatives, monitoring/management options, predisposing factors, and the probability of the interaction based on the strength of evidence available in the literature.

Results Of 31 DDIs considered to be high risk, the panel approved a final list of 15 interactions. Panelists agreed that this list represented drugs that are contraindicated for concurrent use, though it does not necessarily represent a complete list of all such interacting drug pairs. For other drug interactions, severity may depend on additional factors, such as patient conditions or timing of co-administration.

Discussion The panel provided recommendations on the creation, maintenance, and implementation of a central repository of high severity interactions.

Conclusions A set of highly clinically significant drug-drug interactions was identified, for which warnings should be generated in all EHRs. The panel highlighted the complexity of issues surrounding development and implementation of such a list.

INTRODUCTION

Medication-related decision support has the potential to reduce morbidity and mortality associated with preventable adverse drug events and improve the quality of patient care.[1 2] A majority of electronic health records (EHRs) employ clinical decision support (CDS) using commercially available medication knowledge bases (KBs).[2] The extent of the benefit of implementing CDS is seldom realized, in part, due to "alert fatigue".[3] Alert fatigue results when a provider, after receiving too many alerts, ignores and/or overrides them, even clinically significant ones. To address the challenges of alert burden and its impact on EHR adoption, the Office of the National Coordinator for Health Information Technology (ONC) commissioned this effort. The goal of the effort described here was to identify a set of critical interactions that can be implemented in KBs for use in EHRs. A secondary goal was to identify the process and barriers that would be involved in successful implementation of such a list of critical drug—drug interactions (DDIs).

BACKGROUND AND SIGNIFICANCE

Previous studies have empirically evaluated the high rates of overriding medication-related CDS alerts, to range between 33% and 96%.[4 5] Studies recommend reducing alert fatigue by lowering the number of alerts presented to clinicians and by increasing alert specificity.[3 6 7] Most KBs tier DDIs based on their severity and strength of evidence but there is little overlap between these KBs on even the highly significant DDIs.[8–10] Further, local customization of KBs is resource intensive, requires special expertise, and is thus rarely undertaken.[11 12] To facilitate this effort this task order from the ONC focused on identifying high priority DDIs that could be used as a minimum standard for successful incorporation of such critical DDIs into EHRs.

METHODOLOGY

An expert panel was convened with representatives from diverse stakeholders in the implementation of medication-related decision support in EHRs. The panel assessed a set of candidate high severity DDIs that should never be concurrently prescribed and could be used as the minimum standard for inclusion in medication-related decision support programs for use in EHRs. For the purposes of this discussion, a DDI was defined as a modification of the effect of one drug when administered with another drug not from the same therapeutic class.

Developing a list of highly clinically significant DDIs

Sources of information considered in developing the list of DDIs included: Partners Healthcare System Medication Knowledge Base (PHS MKB); commercial medication KBs such as Micromedex; First Data Bank (FDB); http://Drugs.com; and academic research papers written by experts in this domain, for example Malone *et al*,[13] Isaac *et al*,[14] Van der Sijs *et al*,[6] and Hansten and Horn.[10 15] We elected to begin the panel discussions using the highest severity DDIs from PHS MKB because there was substantial variation among sources regarding high severity interactions. Additionally, Partners' DDIs have been extensively used enterprise-wide in clinical practice, and included consideration of many of the above resources for assigning severity.

DDIs in the PHS MKB

The candidate list of DDIs was derived from the medication KB currently employed at PHS. The centralized KB is utilized to generate CDS for DDIs in clinical practice at two large academic medical centers and at primary care clinics that use the in-house developed EHR. This list was developed over several years of in-house customization, based on feedback from clinical end-users and maintained by a team of pharmacists who review the literature evidence and severity ratings in vendor medication KBs to periodically assign the severity rating to keep the list current. Further, a content committee periodically reviews these ratings based on clinical alert logs to assess whether certain interactions need their severity levels to be up- or downgraded. In the PHS MKB, DDIs are documented as drug pairs, expressed with their generic names. DDIs are tiered into three levels depending largely on the severity of the interaction. Each level is presented differently and implies different capabilities for overriding. Level 1 consists of the most serious, life-threatening interactions implemented as "hard stop" alerts that require a clinician to either cancel the order he or she is writing or discontinue the pre-existing, interacting medication order. Level 2 DDIs are of moderate severity and a reason needs to be provided in order to override the alert. Level 3 alerts are the least serious interactions which are presented as non-interruptive or information alerts. Of the 3327 DDI pairs in the PHS KB, 195 DDIs pairs are Level 1, 1561 are Level 2, and 1572 are Level 3 interactions. A medication knowledge committee periodically reviews recommendations from end users to modify the rules in the PHS MKB.[5 7] Given that the PHS MKB has previously been evaluated for coverage of critical DDIs and is periodically tailored based on provider responses in clinical practice, the Level 1 alerts served as a good starting point for the candidate DDIs to be considered in this discussion.

Building a starter set of DDIs using the PHS MKB

In order to facilitate the panel process, we extracted the highest severity interactions or Level 1 DDIs from the PHS MKB. Two clinical pharmacists who had expertise in medication KBs and clinical informatics and one physician with experience in KB engineering and pharmacology, reviewed this list. To consolidate the DDIs, ingredient level pairs were aggregated into appropriate therapeutic, pharmacological or structural classes. For example, the two Level 1 interactions—(i) omeprazole with atazanavir, and (ii) rabeprazole with atazanavir—were converted to a single class-based interaction because both omeprazole and rabeprazole belong to the same pharmacological class, "proton pump inhibitors". Consideration of pharmacodynamic and pharmacokinetic properties also helped in the derivation of appropriate classes for representing the DDIs. We consulted a variety of MKBs, such as Micromedex, FDB, http://Drugs.com, and academic research papers written by experts in this domain (eg, Malone *et al*,[13] Isaac *et al*,[14] Van der Sijs *et al*,[6] and Hansten and Horn[10 15]) to derive the appropriate level of the interaction and membership within a drug class. Using this process, 195 drug–drug pairs were consolidated into a total of 31 interaction pairs, with 12 drug–drug (eg, tranylcypromine–procarbazine), 12 drug–class (eg, atazanavir–proton pump inhibitors), and 7 class–class (eg, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors) interactions.

Expert panel

Twenty-one subject matter experts with experience in the development, maintenance and implementation of medication-related decision support in EHRs were invited to participate on the panel. Diversity of expertise was important in the selection of the panel so as to include a broad array of perspectives. Clinical experts consisted of both practicing physicians and pharmacists who brought real world experience to the discussion. We invited experts to represent medication KB vendors, EHR vendors, proprietary and in-house KB developers, and academic medical centers. Several KB vendors and EHR vendors had pharmacists and providers on their teams who further contributed to the clinical expertise on the panel. In addition, we invited representatives from federal and private agencies involved in the regulation of medication use, such as the Food and Drug Administration (FDA) and the American Society of Health-System Pharmacists. A more detailed description of the participating institutions and panelists is available in table 1.

Each panelist independently assessed all interactions based on the predicted clinical outcome or consequence of the interaction, the severity levels assigned to them across various medication KBs, availability of therapeutic alternatives, monitoring/management options, predisposing factors, and the probability of the interaction based on the strength of evidence available in the literature. The panel also made suggestions regarding specific drugs that should be considered for either addition or deletion under a specific drug class for each candidate DDI. Two rounds of panel discussions were convened to seek consensus.

Ratings from KB vendors

KB vendors are routinely involved with conducting reviews of the evidence in the literature to maintain their product databases and are most up to date with the DDI literature. Three commercial KB vendors, Wolters Kluwer (Medi-Span), FDB, and Cerner Multum, hold a majority of the market share in the area of medication KBs in the USA and participated on the panel. In addition, since the intent of this work was to provide a set of interactions that could be integrated with existing KB solutions, we requested each KB vendor to rate the interactions. Ratings were based on a 9-point scale, with 1 corresponding to "*not at all important*", 5 to "*equivocal*", and 9 to "*extremely important*". KB vendors' ratings were used to calculate average scores by summing the rating from each vendor and dividing the sum by 3; interactions that scored <6 points were removed from the list

Table 1 Characteristics of participating institutions and panelists

Characteristics of participating institutions/panelists	Count
Type of institution	
1. Academic medical center:	5
University of Washington	
University of Arizona	
Columbia University	
Erasmus University Medical Center	
University of Iowa	
2. Integrated healthcare systems with in-house developed knowledge bases:	2
Partners Healthcare	
Veterans Administration	
3. Commercial knowledge base providers:	5
First Data Bank	
Cerner Multum	
Wolters Kluwer (Medi-Span)	
Lexi-Comp	
Thompson-Reuters	
4. Federal or private agencies for the regulation of medication use:	2
American Society of Health System Pharmacy	
Food and Drug Administration	
Clinical/non-clinical role of panelists	
Physicians	7
Pharmacists	13
Product manager	1

because these were considered to be of low clinical significance by the vendors.

RESULTS

From the list of 31candidate DDIs, 16 were accepted by the panel. Of the 16, one interaction, between "linezolid and triptans", was rejected based on a low score provided by KB vendors and was deleted from the final list. Thus, the final list consists of 15 DDIs which represent drugs that should never be co-prescribed and is presented in Table 2. Table 3 lists the DDIs that were deleted from the candidate list and the reasons for their deletion. Table 4 describes the ratings of the KB vendors for the 16 DDI pairs that were accepted.

Modifications recommended by the expert panel

The panel reviewed the initial list with the goal of agreeing upon a list of DDI that represented interacting drug pairs that should not be co-prescribed. From the point of view of implementation, these interactions would always generate alerts in an EHR and receive the highest level of severity rating in medication KBs. Keeping this definition as a guiding point, the panel assessed the suggested list of DDIs, and modifications to the list are discussed below.

Five DDIs (ID #1, 2 10, 17, 19) were discarded, because they were considered to be therapeutic duplications rather than DDIs. A therapeutic duplication is the use of agents from the same chemical family or therapeutic class. Panelists came to consensus that therapeutic duplications should be tracked and alerted separately from DDIs.

Five DDIs (ID #9, 13–15, 18) were demoted to a lower level of severity. DDI #9, between *"gemfibrozil and statins"*, was demoted because panelists pointed out that co-prescribing these medications was common practice, and is sometimes clinically indicated, even though it carries some risk. Only one member of the drug class of statins, cerivastatin, is associated with very high rates of damage to the skeletal muscles or rhabdomyolysis. However, since cerivastatin has been taken off the market, the decision to co-prescribe other statins with gemfibrozil depends on whether the benefits outweigh the risks. Thus, DDI #9 was demoted to a lower level of severity and taken off of the list. DDIs 13–15—*"linezolid—sympathomimetic drugs"*, *"metformin—contrast media"*, and *"miglitol—digestive enzyme"*—did not meet the strict criteria of never being co-administered, and hence were deleted from this list. DDI #18, between *"nitrates and phosphodiesterase (PDE) type 5-inhibitors* (eg, sildenafil, vardenafil and tadalafil)" results in increased levels of cyclic guanosine monophosphate by both nitrates and 5-PDE inhibitors. Panelists demoted this drug interaction because these drugs are often co-prescribed and the interaction can be prevented by appropriately timing their co-administration.

Three DDIs (#5, 24, 29) were deleted because either the object or precipitant drug was no longer available to be prescribed in the US market. One DDI (#26), between *"statins* (except pravastatin and rosuvastatin) *and telithromycin"* was subsumed due to the expansion of DDI #25 to include all drugs in the class of statins, with the exception of cerivastatin which is off-market.

Ratings provided by KB vendors

Three commercial KB vendors, namely, FDB (National Drug Data File Plus), Wolters Kluwer (Medi-Span), and Cerner Multum rated the final set of 16 interactions. The interaction between *"linezolid and triptans"* (DDI #12), was deleted from the list because it received a mean rating of 5.3 and was below the predetermined threshold of 6 for being included in the list. In addition, there was no corroborating literature evidence supporting this interaction, which may have resulted in its low rating by KB vendors. In addition to the ratings, KB vendors provided guidance on the membership of drug classes included in an interacting pair based on their experience with their own products. These recommendations were used to create the final list of suggested drug members that is presented in table 2. A description of the ratings and average scores provided by the KB vendors is provided in table 4.

The panel identified gaps in publicly available medication terminology concepts for describing pharmacokinetic drug classes. Another gap identified by the panel was the lack of a comprehensive and reliable knowledge source to determine membership of these drug classes. Two out of the three KB vendors mentioned that they did not rely on the FDA list for a complete list of members within these drug classes and instead conducted internal reviews to make decisions on them. We describe this finding in greater detail in the discussion of these and other gaps that would pose as barriers to the successful implementation of the high-severity DDI list in EHRs.

DISCUSSION

We identified a minimum starter set of DDIs which should be classified in all medication KBs as high severity and implemented for decision support in all EHRs. The DDIs identified by the panel represent a clinically important group because they have a high potential for patient harm, and are agents that are contraindicated for co-administration. The list suggested here may not be complete but represents a high proportion of DDIs that fall into this category. Further, some interactions that are clinically important and deserve a high severity rating may have been ruled out by the panel because they did not meet the strict criteria of drug pairs that are contraindicated to be prescribed together and where the risk definitely outweighs the benefit offered by co-prescription. The DDIs that are in the final list identified by the panel represent a very small proportion, probably <0.2%, of DDI alerts that are generated in clinical practice.[7] There would be hardly any increase in workload since these alerts would come up rarely. From an implementation perspective, in a scenario where alert fatigue is at a maximum and a clinician chooses to ignore all alerts, this list should probably constitute an additional layer of response from the clinician before being overridden. For example, if clinicians are allowed to override all alerts irrespective of severity levels, then one way of making sure they have not ignored these interactions is to require them to provide a reason for overriding an alert related to co-prescription of the drugs contained in this list. This list identifies interactions that meet the stringent criteria of being both clinically severe and drugs that should not be concurrently prescribed. It is not a comprehensive list but in turn an attempt to describe what could be included in such a starter set and how it can be developed. Since the vast majority of DDI alerts that are generated in most EHRs may not be on this list, alert fatigue will still occur if the remainder of DDI alerts are presented to prescribers. To manage this, there is a need to determine which of the remaining DDI alerts should be presented in a non-interruptive manner and which can be removed from the KB.

Previous studies have identified lists of critical DDIs for specific classes of agents or drugs exhibiting specific mechanisms of interaction.[18–21] More broad based efforts, by Malone *et al*, have previously resulted in a list of high severity interactions

Table 2 List of candidate drug—drug interactions (DDIs) discussed and the final pairs accepted by the expert panel as critical DDIs

#	Candidate drug—drug interaction pair (object—precipitant drug/class)	Status	Considerations suggested by the expert panel	Final DDI pair and suggested membership*	
				Object class	Precipitant class
3	Amphetamine and derivatives—MAO inhibitors	Accepted	Consider downgrading membership of selegiline due to its selective MAO-B inhibition; only at higher doses does it lose specificity and inhibit MAO-A	Amphetamine derivatives: Dexmethylphenidate Dextroamphetamine Methylphenidate Lisdexamefetamine Methamphetamine Phendimetrazine Pseudoephedrine Amphetamine Benzphetamine Diethylpropion Phentermine Atomoxetine	MAO inhibitors: Tranylcypromine Phenelzine Isocarboxazid Procarbazine Selegiline
4	Atazanavir—gastric pH alkalizing agents (proton pump inhibitors (PPIs) + H_2 blockers)	Accepted	1. Only include PPIs and remove H_2 blockers from precipitant class based on literature evidence 2. Add dexlansoprazole to precipitant class	Atazanavir	Proton pump inhibitors (PPIs): Omeprazole Lansoprazole Pantoprazole Rabeprazole Esmoprazole
6	Febuxostat—azathioprine/ mercaptopurine	Accepted	No suggestions made	Febuxostat	Azathioprine and mercaptopurine
8	Fluoxetine—MAO inhibitors	Accepted	1. Expand object class to include other SSRIs instead of only fluoxetine 2. Expand object class to include serotonergic agents	Selective serotonin reuptake inhibitors (SSRIs): Fluoxetine Paroxetine Citalopram Escitalopram Sertraline Fluvoxamine Duloxetine Nefazodone Desvenlafaxine Milnacipran Venlafaxine	Monoamine oxidase (MAO) inhibitors: Tranylcypromine Phenelzine Isocarboxazid Procarbazine Selegiline
11	Irinotecan—ketoconazole	Accepted	Modify precipitant class to include strong CYP3A4 inhibitors†	Irinotecan	CYP3A4 inhibitors† Protease inhibitors: Ritonavir Nelfinavir Atazanavir Indinavir Saquinavir Amprenavir Darunavir Lopinavir Tipranavir Fosamprenavir Saquinavir Macrolides: Clarithromycin Erythromycin Telithromycin Amiodarone Verapamil Diltiazem Azoles: Ketoconazole Itraconazole Fluconazole Voriconazole Nefazodone Aprepitant Cimetidine
16	Narcotic analgesics—MAO inhibitors	Accepted	Insufficient evidence to add fentanyl derivatives (sufentanyl, alfentanyl) to the object class.	Narcotic analgesics: Meperidine Methadone Tapentadol Fentanyl Tramadol Dextromethorphan	MAO inhibitors: Tranylcypromine Phenelzine Isocarboxazid Selegiline Procarbazine

Continued

Table 2 Continued

#	Candidate drug—drug interaction pair (object—precipitant drug/class)	Status	Considerations suggested by the expert panel	Final DDI pair and suggested membership*	
				Object class	Precipitant class
20	Tricyclic antidepressants (TCAs)—selegiline	Accepted	1. No evidence of interaction when selegiline is administered transdermally; consider route specificity 2. Expand precipitant class to MAO-inhibitors	Tricyclic antidepressants (TCAs)	MAO inhibitors: Tranylcypromine Phenelzine Isocarboxazid Selegiline Procarbazine
21	QT prolonging agents—QT prolonging agents	Accepted	1. Include all *high risk* category drugs from http://www.torsades.org ‡ 2. Remove drugs that are off-market or not available in the United States—astemizole, levomethadyl, mesoridazine, probucol, sparfloxacin, and terfenadine as they are off market. Cisapride may be available on an investigational, limited-access basis 3. Add nilotinib which has a black box warning regarding QT-prolongation and sudden death	QT prolonging agents‡	QT prolonging agents‡
22	Ramelteon—fluvoxamine	Accepted	1. Limit precipitant class to strong CYP 1A2 inhibitors: fluvoxamine, amiodarone, ticlopidine, and ciprofloxacin 2. No literature available for other CYP1A2 inhibitors	Ramelteon	Specific CYP1A2 inhibitors:† Fluvoxamine Amiodarone Ticlopidine Ciprofloxacin
23	Rifampin—ritonavir	Accepted	1. Expand the object class to include only strong CYP3A4 Inducers† 2. From the above list remove CYP3A4 inducers like glucocorticoids, troglitazone, modafinil, all barbiturates, and pioglitazone since no literature supporting their interaction 3. Include rifapentine and bosentan 4. Expand precipitant class to include all protease inhibitors 5. Remove weak inducers like oxcarbazepine 6. Efavirenz and nevirapine interact with only some protease inhibitors and are indicated for concurrent use in most combinations 7. One KB vendor suggested further limiting the object class to include only rifampin and St John's wort in the object class as other inducers can be safely given by just adjusting dosages	Strong CYP3A4 inducers:† Bosentan Rifapentine Carbamazepine Rifabutin Rifampin St John's wort	Protease inhibitors: Ritonavir Amprenavir Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Saquinavir Tipranavir
25	HMG Co-A reductase inhibitors Protease inhibitors	Accepted	1. Expand precipitant class to include CYP3A4 inhibitors 2. Remove cerivastatin due to off-market status from object class 3. Remove atorvastatin from object class since magnitude of interaction is less than for other statins	HMG Co-A reductase inhibitors Simvastatin Lovastatin	CYP3A4 inhibitors† Protease inhibitors: Indinavir Saquinavir Tipranavir Ritonavir Nelfinavir Atazanavir Amprenavir Darunavir Lopinavir Macrolides: Clarithromycin Erythromycin Telithromycin Amiodarone Verapamil Diltiazem Azoles: Ketoconazole Itraconazole Fluconazole Voreconazole Nefazodone

Continued

Table 2 Continued

#	Candidate drug–drug interaction pair (object–precipitant drug/class)	Status	Considerations suggested by the expert panel	Final DDI pair and suggested membership*	
				Object class	Precipitant class
27	Telithromycin–ergot alkaloids and derivatives	Accepted	1. Modify object class to CYP3A4 inhibitors 2. Remove from object class: amiodarone, verapamil, diltiazem, fluconazole, nefazodone, aprepitant, and cimetidine due to lack of evidence 3. Remove ergoloid mesylates from precipitant class due to lack of vasoconstrictive properties	CYP3A4 inhibitors† Protease inhibitors: Indinavir Saquinavir Tipranavir Ritonavir Nelfinavir Atazanavir Amprenavir Darunavir Lopinavir Macrolides: Clarithromycin Erythromycin Telithromycin Azoles: Ketoconazole Itraconazole Voreconazole	Ergot alkaloids and derivatives: Ergotamine Methylergonovine Dihydroergotamine Ergonovine
28	Tizanidine–ciprofloxacin	Accepted	Modify precipitant class to include CYP 1A2 inhibitors	Tizanidine	CYP 1A2 inhibitors:† Ciprofloxacin Fluvoxamine Mexiletine Propafenone Zileuton Amiodarone Ticlopidine
30	Tranylcypromine–procarbazine	Accepted		Tranylcypromine	Procarbazine
31	Triptans–MAO inhibitors	Accepted	1. Keep only three triptans (sumatriptan, zolmitriptan, and rizatriptan) for object class 2. For precipitant class include moclobemide and methylene blue	Triptans: Sumatriptan Zolmitriptan Rizatriptan	Monoamine oxidase (MAO) inhibitors: Tranylcypromine Phenelzine Isocarboxazid Moclobamide Methylene blue

*Membership is suggested but not intended to represent every member in the drug class. Specific exceptions, as suggested by the panel, are described where necessary in the column labeled "Considerations suggested by the expert panel".
†CYP-450 inhibitors and inducers obtained from the list provided by the FDA[16] and Flockhart's table from the University of Indiana School of Medicine.[17]
‡http://www.torsades.org (accessed 29 Jul 2011).

intended for use in the outpatient setting.[13] The effort described here differs from these efforts in scope and the intended use of the proposed DDI list. Malone *et al* derived their initial list of DDIs from four drug compendia and not from medication KBs currently employed for decision-support by EHRs. This may be because the focus of their study was limited to community and ambulatory pharmacy settings rather than all EHRs, which is the focus of the effort described here. This limitation resulted in the exclusion of interactions related to drugs, such as halothane or dopamine, which are not routinely dispensed in the ambulatory pharmacy setting, but are commonly administered to inpatients. We elected to consider all types of drugs because we wanted to develop a set of interactions that could be generalized across EHRs used in both the inpatient and ambulatory settings. Malone *et al* utilized a small panel of experts, including two physicians, two clinical pharmacists, and an expert on drug interactions, to vet these interactions. Twenty-one panelists participated in this study; they represented diverse perspectives on the use, development, and implementation of medication-related decision support. In addition, this effort benefited from the long experience and commitment at our own institution to the development and maintenance of the Partners MKB and its use in driving CDS in diverse clinical settings—inpatient and outpatient, community and academic medical centers, and Computerized Provider Order Entry (CPOE) and other clinical information systems. A previous study employed a similar panel-based approach to identify critical interactions for DDI checking and duplicate therapy checking within CDS systems. This study was limited in assessing only those interactions that are available in the Partners MKB, without consideration of the additional knowledge sources described here.[22] A recent evaluation compares leading approaches to critical DDI lists and suggests that the generation of the list described here has the potential to represent an important step forward in standardizing critical DDIs across EHRs and in ensuring that the most clinically important interactions are being seen by all providers.[23]

Utilization of a large review panel with diverse expertise in medication-related decision support provided credibility to this list which could serve as a minimum set of critical DDIs. This list and the methods employed here could also serve as a starting point for additional DDI work that would have more impact on both alert fatigue and consequent patient safety outcomes.

Such a list, if implemented in EHRs, can standardize the process of identification of critical DDIs and save others the effort of doing this work. Further, by mandating alerting against the most critical DDIs in addition to tailoring the list for only the most significant ones that warrant interruption, we can prospectively change practice and prevent unintended consequences at the bedside.

In addition to vetting the list of contraindicated drug pairs for implementation in EHRs, the expert panel also provided insights

Table 3 List of candidate drug–drug interactions (DDIs) not accepted by the expert panel

#	Candidate drug–drug interaction pair (object–precipitant drug/class)	Status	Considerations suggested by the expert panel
1	Abatacept–tumor necrosis factor (TNF) inhibitors	Deleted	Therapeutic duplication not a DDI
2	Abatacept–interleukin-1 receptor antagonist	Deleted	Therapeutic duplication not a DDI
5	Aurothioglucose–artemether + lumefantrine (coartem)	Deleted	Coartem has off-market status
7	Febuxostat–theophylline	Deleted	Only a theoretical interaction with no corroborating evidence
9	Gemfibrozil–statins	Deleted	Delete as clinical benefit of co-prescribing outweighs risk
10	Indinavir–atazanavir	Deleted	Therapeutic duplication not a DDI
12	Linezolid–triptans	Deleted	Deleted due to low rating score by knowledge base vendors
13	Linezolid–sympathomimetic drugs	Deleted	Does not meet criteria for contraindicated DDI
14	Metformin–contrast media	Deleted	Does not meet criteria for contraindicated DDI
15	Miglitol–digestive enzymes	Deleted	Does not meet criteria for contraindicated DDI
17	Natalizumab–immunosuppressants	Deleted	Therapeutic duplication not a DDI
18	Nitrates–5 phosphodiesterase type (PDE) inhibitors	Deleted	Does not meet criteria for contraindicated DDI
19	Pentostatin–fludarabine	Deleted	Therapeutic duplication not a DDI
24	Sodium oxybate–CNS depressants	Deleted	Consider deletion since sodium oxybate is not used in routine practice
26	HMG Co-A reductase inhibitors–telithromycin	Subsumed	Merged with DDI #25 due to expansion of precipitant dose
29	Tranylcypromine–furazolidone	Deleted	Consider deletion since furazolidone is no longer available on the US market

into the pragmatic challenges that might encompass the development and implementation of such a list. These are detailed below.

Gaps in assigning drug class membership for pharmacokinetic interactions

The panel suggested an objective assessment of drug membership for a DDI pair, especially those interactions that are pharmacokinetic in nature, based on their effects on the human cytochrome (CY) P-450 system, for example 3A4 inhibitors or 1A2 substrates. Specific modifications have been outlined in table 2. The incorporation of drug classes based on the CYP-450 system represents a more pragmatic approach to representing and maintaining drug interaction knowledge in providing medication-related CDS. For pharmacodynamic interactions however, the existence of pharmacologic variability within a class can cause a DDI to affect only some but not all the drugs in a class.

A key issue from the informatics perspective is that an important gap exists in representing these classes using Federal Medication Terminologies, such as RxNorm and the National Drug File–Reference Terminology. Neither of these terminologies is currently capable of representing concepts such as "CYP-450 3A4 inhibitors" or "CYP-450 1A2 substrates". This corroborates the findings of Bodenreider *et al*, who evaluated the mapping of drug classes used in representing DDIs to the Unified Medical Language System (UMLS) concepts and found that 17% of the names could not be mapped to any particular class. This implies that these classes are not represented in any of the UMLS source vocabularies, including SNOMED and National Drug File–Reference Terminology. A large majority of the unmapped concepts referred to the metabolism of the drugs, related to a particular enzyme of the CYP-450 family. In addition, there was lack of representation of UMLS concepts that could be used for drug classes, such as "drugs known to prolong the QTc interval", etc.[24] This is another concept that is employed in the high-priority DDI list which cannot be represented using current medication terminologies. Appropriate implementation would require bridging these gaps to allow adequate representation of drug classes.

Defining accurate and complete membership of drugs encompassed within pharmacokinetic drug classes is another critical gap. We examined a number of references seeking a complete list for determining the membership under these drug classes. None of the widely used sources, even some of the most authoritative such as the FDA,[25] Flockhart's[16] table on CYP-450 drug interactions, or Hansten and Horn,[15] provided a complete list of drug members for these classes. Future work should focus on deriving consensus on membership underlying these drug classes so as to promote adequate representation of the drug class concepts.

Table 4 Ratings provided by commercial medication knowledge base vendors on the final set of critical DDIs

DDI#	DDI pairs	First DataBank–NDDF Plus	Cerner Multum	Wolters Kluwer (Medi-Span)	Average score
3	Amphetamine and derivatives–MAO inhibitors	7	9	9	8.33
4	Atazanavir–PPIs	7	8	8	7.66
6	Febuxostat–azathioprine/mercaptopurine	7	9	9	8.33
8	SSRIs–MAO inhibitors	8	9	9	8.66
11	Irinotecan–CYP3A4 inhibitors	6	9	7	7.33
12	Linezolid–triptans	6	5	5	5.33
16	Narcotic analgesics–MAO inhibitors	8	9	7	8
20	TCAs–MAO inhibitors	6	9	7	7.33
21	QT prolonging agents–QT prolonging agents	6	9	8	7.66
22	Ramelteon–CYP 1A2 inhibitors	5	9	7	7
23	CYP 3A4 inducers–protease inhibitors	5	9	8	7.33
25	HMG Co-A reductase inhibitors–CYP 3A4 inhibitors	5	9	8	7.33
27	CYP 3A4 inhibitors–ergot alkaloids and derivatives	7	9	8	8
28	Tizanidine–CYP 1A2 inhibitors	8	9	8	8.33
30	Tranylcypromine–procarbazine	7	9	4	6.66
31	Triptans–MAO inhibitors	7	9	7	7.66

Need for specific criteria to assess critical interactions

Previous studies have identified the lack of standardized criteria for evaluating the severity and clinical significance of DDIs. Two recent studies, one by Wang *et al*[17] and the other by Olvey *et al*,[26] have identified the low rate of overlap (5% and 13%, respectively) among drug compendia for even the most clinically significant interactions. The authors concluded that the lack of overlap existed due to differences in criteria for assessing the severity and level of documentation, among medication KBs, for even the highest severity interactions.

The lack of uniformity across KBs makes it difficult to identify a single list of DDIs with high clinical significance. Panelists cited the MKB developed in the Netherlands by the Royal Dutch Association for the Advancement of Pharmacy as an example of a nationally implemented DDI database. The panel recommended the development and maintenance of explicit editorial guidelines to facilitate a standardized severity assessment process based on criteria of evidence supporting the DDI, clinical relevance of potential adverse reaction resulting from the DDI, assessment of risk factors, and probability of the interaction. The methodology of evaluation described here paves the way for such a consensus process.

Lack of primary literature supporting the evidence for DDIs

Gathering empirical evidence from the literature was a barrier in being able to assess the likelihood of an interaction, a major criterion for assessing the significance of a DDI. We observed that most of the available literature was in the form of documented case reports or clinical studies with drugs belonging to other closely related drug families, or package inserts. The information contained in these package inserts is often incorrect or too conservative for use to assign DDIs in a KB. Moreover, these interactions are not updated regularly to reflect current knowledge. The reason for lack of proper clinical literature contradicting the manufacturer's information is that if the label identifies a certain agent as contraindicated with another agent or in a particular disease state, it is hard for researchers to justify doing clinical trials to empirically test these interactions. Another problem was that while theoretically an interaction may be significant, empirical evaluation may suggest otherwise. Thus, more often than necessary, KB providers have to rely on package inserts to make determinations on DDIs, which may result in overestimating the severity of a large majority of drug interactions.[27]

Poor use of predisposing patient risk factors

Consideration of patient characteristics and co-morbidities is needed to improve the specificity of DDI alert logic. KB vendors pointed out that utilization of these characteristics in conjunction with the drug interactions logic would have a large effect on improving the specificity of alerts. However, despite the knowledge on risk factors that predispose a patient to particular interaction, this information is seldom employed. This is because in the current state, EHR implementations typically do not employ logic that uses both patient characteristics in conjunction with the medication profile of the patient to generate alerts. Information that is routinely present in EHRs, such as patient age, gender, and co-morbidities that mitigate or increase the risk of an interaction, should be used to contextualize the alert for a specific patient to reduce the generation of clinically insignificant alerts. Greater collaboration is needed between EHR vendors and KB vendors to improve alert logic based on patient context information and provider behavior in response to alerts. This information sharing can be beneficial to both parties. The EHR vendors will see greater user satisfaction due to a possible decrease in alert fatigue, and the KB providers will be able to improve their products and prune the alerts based on how they are actually used in clinical practice.

Resource intensive process

Developing and maintaining a list of high priority DDIs is a resource intensive process. Panelists expressed concern regarding maintenance of two separate KBs, should such a list be implemented in addition to what is employed by EHRs. Panelists suggested that the process for evaluating DDIs should be centralized so that the burden of resources needed could be shared and such a list could serve a larger public good. Names of organizations that were suggested as neutral entities for maintaining the list of DDIs, were the American Society of Health-System Pharmacists, the College of American Pathologists, the National Library of Medicine, or the US Pharmacopoeia. An alternate suggestion was to authorize the organization that undertook its development and have periodic discussions with KB vendors and feedback from clinicians to modify the list based on new evidence that becomes available and on physician acceptance of alerts in actual clinical settings. Either approach would involve creating a clearing house of information where KB vendors and the institution responsible for maintaining the standard list could make decisions on its content, such as suggesting severity levels based on previously agreed upon criteria and being able to nominate, elevate, or demote interactions from the list. Further, the critical set of alerts should contain information on further stratification based on patient context variables, which implementers could tune based on the level of specificity of alerts relevant to the clinical setting. Such assessments could be further guided by real-world clinical input through implementation in EHRs, to assess outcomes associated with the implementation of this set of DDIs. Further, the heuristics, editorial guidelines, severity levels, and other definitions adopted by the group, in developing the DDI list, should be transparent and should take into consideration the current systems followed by KB vendors to facilitate easy integration with their own databases without the need to for re-programming.

Limitations

This study had a number of limitations. We had limited resources and a strict schedule so that we could not perform a comprehensive literature review for each DDI evaluated. Despite this limitation, we identified a small set of interactions with strong consensus, and described a process that could be utilized to gain consensus on assessing additional DDIs. The expert group was limited in size, but included many of the leading experts in this domain and it represented a diverse set of perspectives. Future work should include analyses of critical DDIs from multiple sources to improve representation of interactions in this list, and a determination of impact on alert override rate.

CONCLUSIONS

EHRs should implement strong safety checks in the medication ordering process to prevent inappropriate co-administration of drugs for the interacting pairs identified in this study. This set of DDIs forms a clinically important set of contraindicated drug pairs that providers should always be alerted for. However, this is a starter set of contraindicated DDIs and the list may not be complete. There are other drug pairs that clinicians and

informaticians should consider alerting on, but they do not fall into the relatively narrow category of drugs that are contraindicated for concurrent use. Future work must also focus on the identification of DDIs that exist in KBs but are not sufficiently corroborated by evidence, so that they can safely be omitted from generating alerts and hence have a more palpable impact on alert fatigue.

This starter set of interactions should be included in all EHR implementations, and should not be inactivated. Such a requirement should be considered as a criterion for "meaningful use" of DDI alerting. Terminological gaps, lack of standardized criteria for DDI assessment, lack of primary literature providing the evidence to assess DDIs, poor patient contextualization of DDIs, and the overall difficulty in terms of the resources needed to perform this task, all represented barriers in this area. However, these barriers are not insurmountable; the recommendations of the panel provide useful guidance in order to overcome these and represent opportunities to advance the field of medication-related decision support, which could have broad benefits.

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