Critical Drug-Drug Interactions for Use in Electronic Health Records Systems With Computerized Physician Order Entry: Review of Leading Approaches

David C. Classen, MD, MS, Shobha Phansalkar, RPh, PhD,†‡ and David W. Bates, MD, MSc†‡*

Abstract: Medications represent the most common intervention in health care, despite their benefits; they also lead to an estimated 1.5 million adverse drug events and tens of thousands of hospital admissions each year. Although some are not preventable given what is known today, many types are, and one key cause which is preventable is drug-drug interactions (DDIs). Most electronic health record systems include programs that can check and prevent these types of interactions as a routine part of medication ordering. Studies suggest that these systems as implemented often do not effectively screen for these DDIs. A major reason for this deficiency is the lack of any national standard for the critical DDIs that should be routinely operationlized in these complex systems. We review the leading critical DDI lists from multiple sources including several leading health systems, a leading commercial content provider, the Leapfrog CPOE Testing Standard, and the new Office of the National Coordinator (ONC) DDI List. Implementation of strong DDI checking is one of the important steps in terms of realizing the benefits of electronic prescribing with respect to safety. Hopefully, the ONC list will make it easier for organizations to ensure they are including the most important interactions, and the Leapfrog List may help these organizations develop an operational DDI list that can be practically implemented. In addition, this review has identified 7 common DDIs that can be the starting point for all organizations in this area of medication safety.

Key Words: drug-drug interactions, clinical decision support, electronic health records, patient safety

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Medications represent the most common intervention in health care, despite their benefits; they also lead to an estimated 1.5 million adverse drug events and tens of thousands of hospital admissions each year. Although most are not preventable given what is known today, many types are, and one key cause is drug-drug interactions (DDIs).[1]

An essential part of any medication prescription or order for a medication is to check the new medication for interactions with the other medications the patient is taking. One example is the interaction between warfarin and trimethoprim-sulfamethoxazole that can cause significant increased effect from the warfarin, potentially leading to serious bleeding. A clinically relevant DDI occurs when the effectiveness or toxicity of one medication is altered by the administration of another medicine or a substance that is administered for medical purposes (to be distinguished from drug-food interactions). Adverse consequences of DDIs may result from either diminished therapeutic effect or toxicity. The potential for clinically important DDIs often can be predicted based on the drug properties, method of drug administration, and patient-specific parameters.[2] Consequently, adverse outcomes resulting from DDIs can be prevented by making patient- and situation-specific assessments and, if appropriate, avoiding concomitant administration by implementing alternative therapeutic strategies or taking precautionary measures such as dosage adjustments and increased monitoring.

From the *Division of Infectious Diseases, University of Utah School of Medicine and CSC, Salt Lake City, Utah; †Division of General Medicine and Primary Care, Brigham and Women's Hospital and Harvard Medical School, Boston; and ‡Partners HealthCare System, Wellesley, Massachusetts.
Correspondence: David C. Classen, MD, MS, 561 East Northmont Way, Salt Lake City, UT 84103 (e-mail: dclassen@csc.com).

CHALLENGES WITH DDI CHECKING

Historically, most DDI checking has been performed by pharmacists using pharmacy computer systems at the time of dispensing, which has some disadvantages—the patient is expecting to get the medication, it often is hard for the pharmacist to reach the physician, resulting in delays, and the pharmacist may not have complete information about the patient. However, with the development of electronic health records (EHRs), this task is now being performed increasingly by physicians as part of computerized physician order entry (CPOE), although pharmacists continue to perform checks before they actually dispense the drugs, which allows a "double check."

This transition has led to a critical reappraisal of this type of clinical decision support and its ability to prevent patients from getting drugs prescribed that can cause serious interactions. A recent study of primarily outpatient pharmacies evaluated how many critical DDIs were picked up in actual practice using simulated scenarios. In that study, only 18 (28%) of the 64 pharmacies correctly identified eligible DDIs and noninteractions. The median percentage of correct DDI responses was 89% (range, 47%–100%) for participating pharmacies.[3] A similar study done in the inpatient setting using EHRs found that only 52.4% of critical DDIs were detected among 62 hospitals with EHRs and CPOE.[4]

Although these studies are recent, this is not a new issue because previous studies have outlined the same problems.[5] Although this is a recurring problem, the causes are complex. Most DDI checking is done with EHRs that are linked to clinical decision support, most of which is supplied by content vendors that supply decision support around an array of medication-related issues, including DDIs. The knowledge in this domain requires updating on a continuous basis, as new interactions are regularly being identified, and new information becomes available about existing interactions. These databases contain exhaustive information that often is hard to customize for local use, and customization is sometimes even contractually precluded. Many organizations implement with little or no customization.[1] The result is that as implemented in most computer systems, DDI checking can be burdensome and workflow insensitive, especially if too many warnings are displayed. In some studies, override rates by physicians have been approximately 90%,[6] although another study by Shah et al[7] demonstrated that with careful selection of which interactions are interruptive, high levels of provider acceptance can be achieved. Furthermore, tiering of DDIs can be extremely

helpful in ensuring that providers accept the truly important interactions.[8]

When too many warnings are displayed, the productivity issues can be sufficiently severe as to cause the DDI checking to be turned off or dramatically reduced with attendant results.[3] These systems also can lead to alert fatigue when providers are so overwhelmed with alerts, many of them false positive, that they begin to ignore all alerts.[3] The same issues also can occur in the inpatient setting and often lead to all DDI alerts being turned off at the physician level and the pharmacist level as well.[9]

BACKGROUND OF LEAPFROG GROUP, LEAPFROG CPOE TESTING STANDARD

The Leapfrog Group is a voluntary program of large employers seeking to mobilize a combination of public awareness and rewards to higher-quality providers to accomplish breakthrough improvements (big "leaps") in patient safety. Members include many of the nation's largest employers and public agencies that buy health benefits for more than 35 million Americans. This group developed a series of health care provider safety standards designed to help employers steer employees to organizations that had implemented patient safety best practices. One of those safety standards was focused on CPOE. The CPOE standard was one of the first Leapfrog safety best practices because medication errors have tragic consequences for so many patients and result in tremendous financial costs.[10] The intent of the Leapfrog CPOE standard is to promote the hospital use of CPOE with clinical decision support that can intercept erroneous and dangerous medication orders and this standard has been formally incorporated in the National Quality Forum's CPOE safe practice.[11] The Leapfrog CPOE Standard is described elsewhere, but its use of a testing protocol in the standard recognizes that it is important to verify the extent to which the CPOE system in use actually intercepts problematic medication orders in many important categories of medication safety problems including a category focused on critical DDIs.[12]

The Leapfrog CPOE evaluation focuses on implemented CPOE applications rather than vendor CPOE applications "out of the box" or "off the shelf" because the implemented system is what the patient actually experiences.[10] The evaluation mimics physician order writing in the hospital, using test patients and a set of test orders. Most hospitals can use a test system so long as it mirrors all the order management functions and decision support in the production system. A Web application for the evaluation is included in the Leapfrog survey Web site to disseminate instructions, test patients, test orders, and capture hospital self-reported evaluation results.[9]

The DDI section of the Leapfrog test focused on serious DDIs as defined by the literature and a panel of experts. The DDIs selected were thought most likely to cause either severe or frequent adverse drug events to patients (i.e., actual events rather than just errors or unsafe situations). The test was initially released in 2008 and used through 2010. The initial results of testing were summarized for 62 hospitals, and these initial hospitals, on average, picked up only 52.4% of the DDIs presented to them during testing.[4] However, over the next 2 years, hospitals did improve results in their tests of DDI checking by more than 25%. User feedback on the test was collected as part of the testing protocol over this period, and the test was updated based on user feedback, literature updates, protocols developed at leading health systems for DDI checking, and critical DDIs identified from third-party content vendors. As with the development of the initial test, all information was presented to an expert panel that then helped develop the new testing pairs of critical DDIs. This resulted in a new DDI section of the updated test that will be released in spring of 2011. The new test has increased the total number of DDI pairs in the test library and increasingly harmonized them with the third-party content vendors, leading health system protocols and increasing the focus on only the most severe DDIs.

BACKGROUND OF RAND ADVANCING CLINICAL DECISION SUPPORT PROJECT

The Office of the National Coordinator for Health Care Information Technology's Advancing Clinical Decision Support Initiative

This initiative was undertaken by the Office of the National Coordinator (ONC) to promote broad Clinical Decision Support (CDS) adoption, dissemination, and effective use of computer-based CDS interventions to facilitate evidence-based clinical practice and meaningful use of health IT. This effort was funded under the Health Information Technology for Economic and Clinical Health Act of 2009.

"Advancing Clinical Decision Support" is a multitask initiative funded by the U.S. ONC for Health Information Technology to promote adoption of CDS in clinical information systems. The focus of this initiative is to promote the alignment of CDS implementation with the newly developed standards for "meaningful use" of EHRs. RAND Corporation, in partnership with Partners Health Care, is responsible for leading the 4 interrelated tasks that constitute this initiative. These tasks are to distill best practices for CDS design and implementation, distill best practices and standards for sharing CDS knowledge, produce an open online platform for sharing CDS knowledge artifacts among EHR vendors and/or provider organizations, develop a "clinically important" DDI list and a legal brief about the liability implications of using the clinically important DDI list, and to develop a process that engages clinical specialties to assess performance gaps that may present as opportunities for incorporation of CDS interventions in EHRs.

This initiative will provide important insights to providers to achieve meaningful use of EHR technology by the incorporation of CDS capabilities. The end goal is for these insights to pave the way for health care reform and transform the way health care is practiced by effectively incorporating CDS interventions that not only foster best practices of care but also are streamlined with the clinicians' workflow.

Approach for the Development of the High-Priority DDI List in the Advancing Clinical Decision Support Project

Recognizing the impact that excessive alerting can have in decreasing the successful adoption of medication-related decision support, the ONC commissioned the development of a starter set of clinically significant DDIs for use in ambulatory EHRs, as part of the national effort for "Advancing Clinical Decision Support" and moving toward meaningful use of medication-related decision support in EHRs. Partners Healthcare in partnership with the RAND Corporation convened an expert panel to identify this starter set of high-priority DDIs.

Medication Knowledge Base Used at Partners Healthcare

To develop and validate a list of high-priority candidate DDIs consisting of the highest severity interactions currently in use at Partners Healthcare System (PHS) were extracted. At Partners, the set of DDIs used to generate alerts fall into 3 levels

of severity: the most severe (level 1), which are "hard stops" that require the physician to cancel one of the orders for the interacting drug pair; moderate (level 2), which can be overridden by the physician if deemed clinically necessary but require the specification of a reason for continuing with the interacting drug pair; and the least severe (level 3), which are informational in nature and thus noninterruptive to the clinicians' workflow. The DDIs are expressed as ingredient level drug concept pairs, and a total of 3327 DDI pairs exist in the knowledge base, of which, 195 DDI pairs are assigned as level 1, 1561 as level 2, and 1572 as level 3.

The DDIs are used to generate alerts in a majority of order entry systems used across the Partners enterprise. In addition to a team of clinical pharmacists, frontline physicians from diverse specialties and entities across the enterprise provide expertise on a centralized Medication Knowledge Committee, which is charged with vetting the clinical content contained in the Partners proprietary drug knowledge base. This committee makes the final adjudication to determine the Partners DDI knowledge base, which differs significantly from some of the commercially available DDI knowledge bases in that it carefully weighs the level of severity at which a DDI should fire so as to minimize interruptions to a physician's workflow during the order entry process and possible alert fatigue.

Methodology Used for the Generation of the High-Priority DDI List

As a starter set, we extracted the highest severity or level 1 DDIs from the PHS knowledge base. To facilitate discussion and provide the most consolidated set of DDIs to vet with the expert panel, we needed to aggregate the ingredient level pairs into appropriate therapeutic, pharmacologic, or structural classes so that multiple pairs could be adequately represented into class-based pairs. This was done by studying the mechanism of the interaction, the type of drug interaction, that is, if the interaction was pharmacodynamic or pharmacokinetic, and by assessing membership of drug pairs in other commercial knowledge base sources, such as Micromedex,[13] First Data Bank,[14] Drugs.com,[15] and academic research papers written by subject matter experts in this domain.[16–19]

Expert Panel for Assessing the High-Priority DDI List

The panel consisted of 21 subject matter experts experienced in the development, maintenance, and implementation of medication-related decision support in EHRs. The candidates represented a diverse set of institutions, such as academic medical centers, commercial knowledge vendors, organizations with medical knowledge bases that were developed and maintained in-house, and federal or private agencies involved in the regulation of medication use. The goal of convening this panel was to validate the list of high-priority DDIs that was developed and to gain insights from the experts' experiences of implementing and tailoring DDIs at their own institutions. To aid the process of determining the clinical significance of the starter set of 31 DDIs, the panelists were provided with the following information for each DDI pair: the mechanism of action of the interaction; the type of interaction, that is, whether it was pharmacokinetic or pharmacodynamic in nature; the warning message to accompany the alert; the clinical outcome or consequence of the interaction; severity level of the interaction as assigned in the afore-mentioned commercial knowledge bases and drug knowledge sources; therapeutic alternatives; management for mitigation of the risk of the interaction; predisposing factors that may increase the risk to the patient for a given interaction; and probability of the interaction. A detailed description of the methodology and the final list of DDIs are described in an upcoming publication.

COMPARISON OF ONC AND LEAPFROG RESULTS FOR DDI CHECKING

In Table 1, we have indicated the overlap between the list of DDIs in the Leapfrog test and those that were considered high-priority DDIs by the expert panel (ONC List), and critical DDI lists from two leading health systems (A&B), from Partners Health System, and from a commercial product. One fundamental difference between the Leapfrog and the ONC DDI lists is the level at which these lists are expressed. Although the Leapfrog list contains specific drug names, dosages, intervals, and routes, the ONC list is only available at the class level with specification of possible drug membership within these classes. In comparing, the members specified in the ONC DDI list, the Leapfrog and ONC DDI lists, agree on almost half of the Leapfrog DDI pairs. The ONC list does not include several pairs that Leapfrog does include that also are included in health system and commercial system lists as well as seen in Table 1. The reasons for these discrepancies are as follows: first, dofetilide and the combination of sulfamethoxazole and trimethoprim, was initially on the list that was presented to the ONC expert panel. The interaction between this drug pair results in an increased risk of cardiotoxicity, for example, QT prolongation, torsades de pointes, and cardiac arrest. The ONC panel recommended that only the highest risk category of drugs be included for membership as object and precipitant drugs for the risk of QT prolongation. The suggested source for membership was a Web site (www.torsades.org) where a list of QT-prolonging drugs is grouped by definite, possible, and conditional risk of torsades de pointes; the combination of trimethoprim and sulfamethoxazole is only listed as one having a conditional risk and hence did not make it on the ONC list. For the same reason, the DDI between ciprofloxacin and sotalol was not approved by the ONC expert panel. Use of ciprofloxacin in combination with a Class III antiarrhythmic agent, such as sotalol, can result in increased risk of QT prolongation, torsades de pointes, or cardiac arrest. However, only sotalol is considered to produce a definite risk, whereas ciprofloxacin is known to possess only a conditional risk. The DDI of indinavir and atazanavir, although initially included in the ONC list, was removed because it was considered a therapeutic duplication by the panel because both agents are antiretrovirals. For the same reason, the interaction between azathioprine and mercaptopurine was discarded; it was considered a therapeutic duplication rather than a DDI because both drugs act as immunosuppressive agents. Four DDIs, between selegiline and methyldopa, between voriconazole and ziprasidone, between alprazolam and ketoconazole, and between quinidine sulfate and itraconazole, were not present at the highest severity level in the PHS knowledge base and hence not vetted by the ONC panel.

There are several other differences that exist between the 2 lists. First, fundamentally, the lists have been designed with very different purposes in mind. The Leapfrog list, as previously mentioned, was designed to verify whether an inpatient CPOE system had the potential to intercept critical DDIs, whereas the ONC list was designed to reduce alert fatigue and describe the most clinically significant, high-priority DDIs that should be implemented "as a minimum" in all ambulatory EHRs. Although both lists contain critical DDIs, the Leapfrog list specifies these as specific drug orders, and the ONC list only describes interaction pairs at the class level. Furthermore, the ONC expert panel deliberated the list of DDIs as not just critical interactions but those drug pairs that should never be concurrently prescribed. Thus, many DDIs, although deemed severe in their clinical significance

TABLE 1. Critical DDI List by Leading Approaches

Drug 1	Drug 2	Found in Leapfrog DDI Test Version 2	Found in Partners Health System Level 1 List	Found in Commercial Product Level 1 list	Found in Health System A Level 1 list	Found in Health System B Level 1 list	Found in ONC Level 1 List
Linezolid 600 mg IV every 12 h	Sumatriptan 25 mg every 4 h as needed for migraines	Yes	Yes	Yes	Yes	Yes	Yes
Methylphenidate 10 mg PO twice daily	Selegiline 5 mg PO twice daily	Yes	Yes	Yes	Yes	Yes	Yes
Fluoxetine 20 mg PO daily	Phenelzine 15 mg PO 3 times daily	Yes	Yes	Yes	Yes	Yes	Yes
Sumatriptan 25 mg every 4 h as needed for migraines	Phenelzine 15 mg PO 3 times daily	Yes	Yes	Yes	Yes	Yes	Yes
Citalopram 20 mg PO daily	Selegiline 5 mg PO twice daily	Yes	Yes	Yes	Yes	Yes	Yes
Paroxetine 20 mg PO every morning	Tranylcypromine 15 mg PO twice daily	Yes	Yes	Yes	Yes	Yes	Yes
Quinidine sulfate 300 mg PO every 8 h	Dofetilide 500 μg PO twice daily	Yes	Yes	Yes	Yes	Yes	Yes
Dofetilide 500 μg PO twice daily	Sulfamethoxazole 800 mg and trimethoprim 160 mg 1 tablet PO twice daily	Yes	Yes	Yes	Yes	Yes	No
Indinavir 800 mg PO every 8 h	Atazanavir 400 mg PO daily	Yes	Yes	Yes	Yes	Yes	No
Ciprofloxacin 500 mg PO twice daily	Sotalol 80 mg PO twice daily	Yes	Yes	Yes	Yes	Yes	No
Alprazolam 0.5 mg PO 3 times daily	Ketoconazole 400 mg PO daily	Yes	Yes	Yes	Yes	Yes	No
Quinidine sulfate 300 mg PO every 8 h	Itraconazole 200 mg PO twice daily	Yes	No	Yes	Yes	Yes	No
Voriconazole 200 mg IV twice daily	Ziprasidone 40 mg PO twice daily	Yes	No	Yes	Yes	Yes	No
Selegiline 5 mg PO twice daily	Methyldopa 250 mg PO 4 times daily	Yes	No	Yes	Yes	Yes	No

and with strong evidence supporting their existence, were not included on the ONC list if the panel deemed there were even infrequent clinical situations where the two drugs should be prescribed together. Much of the clinical harm caused by DDIs is caused by these relatively lower-ranked interactions because only those drugs should never be given together.

The ONC list is clearly much larger than the Leapfrog list, and this may reflect several issues: the importance for the Leapfrog list to be harmonized with both commercial and health systems lists, to be more concise so that health systems do not over alert, and the Leapfrog list reflects a list that has been pared down so that it can only include those drugs that are on most hospital formularies such that the test will be broadly applicable. The larger ONC list may serve as a library of future DDIs for the annual updating of the Leapfrog DDI list, and the Leapfrog list will likely remain constrained to a smaller list that is operational with most hospitals that take the test and thus may lag behind the broader focused and less specific ONC list.

RECOMMENDATIONS FOR LEAPFROG DDI FUTURE AREAS OF FOCUS

The Leapfrog DDI focus areas will continue to be updated on a yearly basis and will survey the DDI level one lists from commercial sources, health systems, and the ONC list as well as DDIs from published studies to create a potential list for its expert panel to review. Wherever possible, it will attempt to harmonize its DDI list with each of these other lists in Table 1. This process will update the library of DDI that Leapfrog will use in its test. Leapfrog will make every effort to give published guidance on this updated list every year to help hospitals understand the areas of focus for the DDI part of the test. Indeed the Leapfrog DDI list might function as a test bed for the ONC DDI list, serving as a feasibility test for DDI pairs on the ONC list.

CONCLUSIONS

Drug-drug interactions cause an important amount of harm, which is largely preventable. However, organizations have struggled with which interactions to display. Most have displayed too many interactions, which can result in alert fatigue and even cause rejection of the underlying systems. The "sweet spot" in this area is to include the important interactions, while not alerting at least in an interruptive fashion on those that are less important. Because hospitals have had to develop these lists of important interactions on their own, this has been a struggle.

The ONC project represents an effort to identify the most serious, or "cannot-miss" interactions, and to make them widely available. For the Leapfrog test to be a good test, it should include the interactions that are most important to improving

care in organizations. Some of these fall into the "cannot miss" group, as is the case in this comparison of the two lists. However, the Leapfrog list is and should be more comprehensive because it includes interactions that are sometimes acceptable but should generally be avoided.

Implementation of strong DDI checking is one of the important steps in terms of realizing the benefits of electronic prescribing with respect to safety. Hopefully, the ONC list will make it easier for organizations to ensure they are including the most important interactions, and the Leapfrog list may help these organizations develop an operational DDI list that can be practically implemented. This review has identified the 7 common DDIs that could be a starting point for all organizations as they focus on this area of medication safety.

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