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Recommendations for Selecting Drug-Drug Interactions for Clinical Decision Support

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Abstract

Purpose—To recommend principles for including drug-drug interactions (DDIs) in clinical decision support.

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Methods—A conference series was conducted to improve clinical decision support (CDS) for DDIs. The Content Workgroup met monthly by webinar from January 2013 to February 2014, with two in-person meetings to reach consensus. The workgroup consisted of 20 experts in pharmacology, drug information, and CDS from academia, government agencies, health information (IT) vendors, and healthcare organizations. Workgroup members addressed four key questions: (1) What process should be used to develop and maintain a standard set of DDIs?; (2) What information should be included in a knowledgebase of standard DDIs?; (3) Can/should a list of contraindicated drug pairs be established?; and (4) How can DDI alerts be more intelligently filtered?

Results—To develop and maintain a standard set of DDIs for CDS in the United States, we recommend a transparent, systematic, and evidence-driven process with graded recommendations by a consensus panel of experts and oversight by a national organization. We outline key DDI information needed to help guide clinician decision-making. We recommend judicious classification of DDIs as contraindicated, as only a small set of drug combinations are truly contraindicated. Finally, we recommend more research to identify methods to safely reduce repetitive and less relevant alerts.

Conclusion—A systematic ongoing process is necessary to select DDIs for alerting clinicians. We anticipate that our recommendations can lead to consistent and clinically relevant content for interruptive DDIs, and thus reduce alert fatigue and improve patient safety.

BACKGROUND AND SIGNIFICANCE

Exposure to potential drug-drug interactions (DDIs) can cause preventable patient harm and requires proper management.[1] Many electronic prescribing and medication information systems include interruptive alerts and non-interruptive information as forms of clinical decision support (CDS) to warn clinicians that potential DDIs exists based on a patient's medication history.[2,3] DDI alerts most commonly occur during the prescriber medication order entry or the pharmacist dispensing/verification process. The Centers for Medicare & Medicaid Services (CMS) included DDI screening in the agency's guidelines for achieving meaningful use of electronic health records (i.e., CMS Meaningful Use Core Measure 2).[4] Today, every pharmacy and increasing numbers of physician offices and healthcare organizations in the United States employ some form of health information technology (IT) that includes DDI alerts.[5]

The content of the vast majority of DDI decision support systems in the United States is created, maintained, and sold by drug knowledgebase vendors that use their own approach for evaluating and classifying the clinical importance of DDIs.[6] Studies have demonstrated substantial variability in DDI alerting performance across electronic prescribing and pharmacy software systems.[7–14] Ubiquitous and low clinical relevance alerts have contributed to considerable clinician frustration and dissatisfaction[15–17] and reported override rates for DDI alerts consistently exceed 90%.[18–20] Commentators have stated that "the current DDI alert system is broken."[14] A systematic and transparent process with ongoing governance and infrastructure is imperative to improve the clinical relevance and consistency of DDI alerts.

To address the aforementioned issues we conducted a conference series to develop specific recommendations to improve the quality of CDS alerts for DDIs. These activities were supported in part by a conference grant from the Agency for Healthcare Research and Quality and donations from health IT vendors. Recommendations by other workgroups were published separately.[21,22] This paper describes recommendations by a workgroup to create a process to establish a standard set of DDIs for CDS.

MATERIALS AND METHODS

As part of a larger conference series to improve the quality of CDS for DDIs, 20 individuals with expertise in DDIs, clinical pharmacology, CDS, and establishing healthcare quality initiatives were invited and agreed to participate. The workgroup's primary goal was to recommend principles and processes for including DDIs in drug safety alerts that would ultimately guide the development and maintenance of a standard set of DDIs for CDS. Members represented diverse backgrounds such as academia, drug knowledgebase vendors, drug information compendia, clinicians, professional societies, and the Office of the National Coordinator for Health IT (ONC); and the Food and Drug Administration.

The workgroup met monthly by webinar from January 2013 to February 2014, with live meetings held in Washington DC (May 2013) and Phoenix, Arizona (September 2013). Recommendations were developed by consensus after completing a literature review on methods and best practices for establishing consensus in decision-making. Draft questions were proposed by two members and the entire group modified and addressed the following key questions:

1. What process should be used to develop and maintain a standard set of DDIs?
2. What information should be included in a knowledgebase of standard DDIs?
3. Can/should a list of contraindicated drug pairs be established?
4. How can DDI alerts be more intelligently filtered?

The focus of this project was drug-drug interactions. We recognize that many other types of interactions (e.g. drug-food, drug-herbal, drug-disease) exist but were considered outside the scope of this project. Many of these interactions share a number of characteristics that are similar, but we did not attempt to address all of the issues across all types of interactions. Recommendations in this paper may be relevant to these other interactions.

RESULTS

Key Question 1: What process should be used to develop and maintain a standard set of DDIs?

A key component of improving the relevance of DDIs is identifying DDIs with clinical consequences warranting interruption of the ordering process. Phansalkar *et al.* identified an initial set of high priority DDIs through an ONC task order that could be used as a minimum standard for electronic health record systems[23] and a set of DDIs that should be non-

interruptive in order to reduce alert fatigue.[24] Because clinical knowledge changes over time and new products are brought to market, an ongoing process is needed with governance and infrastructure to ensure that a standard set of DDIs is regularly updated and reflects current evidence and newly discovered DDIs. This undertaking is not trivial and requires substantial resources.

In light of these issues and ongoing challenges, we recommend forming a national consensus panel of experts to create and maintain a standard set of clinically relevant DDIs for CDS systems, with oversight by a national organization to ensure that the process is transparent, systematic, and evidence-driven (Figure 1). Key elements for developing trustworthy clinical recommendations include ensuring that expert panelists consider relevant evidence, including relevant stakeholders, providing opportunities for public comment, documenting panelist and external reviewer comments and responses, and actively managing conflicts of interest.[25–28]

National Process with Centralized Oversight—We recommend selecting a centralized organizer or convener, such as an academic unit or a professional association or organization (e.g., American Society of Health-System Pharmacists, American Society for Clinical Pharmacology and Therapeutics, American Medical Informatics Association, etc.) with full-time staff, to serve as the driving force to convene the panel and disseminate information.[29,30] The goal should be to maintain the evidence base and decision algorithms for the ‘public good’ and, therefore, public funding must support this venture to align and promote collaboration among the public and private sectors. We recommend a standard set of DDIs for use in CDS should be created and maintained independent of reimbursement decisions. This evidence base could be established so that it is accessible as a web service, so that it could be utilized by many providers and healthcare systems.

We recommend that a panel of experts be created and include individuals with clinical expertise and skills in evaluating DDIs. Because of concerns of being too prescriptive we recommend that members of the inaugural panel define the following attributes: the appointment process; terms of membership; procedural rules (e.g., voting policies and procedures); framework for executing the steps involved in grading recommendations; policies for managing potential conflict of interest; and the policies and procedures of a comprehensive and transparent DDI selection process (e.g., methods for evidence summary and presentation, balloting procedures).

Use of expert advice is particularly important because the types and quality of evidence available for DDIs differ substantially from other areas of clinical practice. Furthermore, research indicates that expert advice improves the acceptance and value of DDI alerts.[15,31] We recommend including individuals with clinical expertise and skills in evaluating DDIs. Furthermore, experts should have a background in clinical pharmacology, pharmacokinetics, pharmacoepidemiology, medication safety, clinical experience in relevant clinical subspecialties, health information technology, and human factors engineering.

Evidence Synthesis—We recommend a systematic process for assembling DDI evidence, similar to approaches used for systematic reviews and practice guideline

development.[32–37] Qualified experts should summarize the evidence and quality assessment for presentation to the national expert panel for deliberation. Another workgroup associated with this initiative has developed a new evaluation tool - the DRug Interaction eVidence Evaluation (DRIVE) instrument—to establish *sufficient* evidence for DDIs that *may* require clinical management.[21] Before widespread use, the instrument should undergo testing and validation. That said, the DRIVE instrument or other approaches should be incorporated into the process to provide clinicians a clear rating of the overall quality of evidence, with graded recommendations for clinical management.[34]

Grading Recommendations for Risk Management—A major challenge in applying this approach to DDIs is defining the hierarchy of graded risk management recommendations in such a way that, despite the often-weak nature of DDI evidence, confidence can be placed in the recommendations to adequately support them.[34,38] It also will be important to present the hierarchy of graded risk management recommendations in a manner that is comprehensible to a wide range of users.[39] The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach has been adapted to DDIs and could be further refined for this process.[21,32,33,35] Although the graded DDI recommendations will be advisory in nature, we expect that the approach used by the organizer/convener will promote trust among prescribers and pharmacists so recommendations can be confidently applied.

Community Feedback on DDI Recommendations—We recommend that a web-based process be created and maintained to solicit input concerning classification of DDIs. Input from numerous stakeholders, including clinicians, healthcare and quality organizations, government agencies, IT vendors, and pharmaceutical companies are strongly encouraged. Broad-based feedback is essential for both maintenance and quality improvement in managing the knowledgebase.[40] It should be easy for prescribers, pharmacists, and other clinicians to submit petitions to the panel to add or re-evaluate drug combinations (e.g., up- or down-grading classification). Requests to remove or add DDIs should be evaluated based on clinical and scientific merits.

Subsequent Evaluation, Re-evaluation, and Updates—Periodic and timely updates of the standard set of DDIs are essential.[41] We recommend at least annual updates, given the dynamic nature of DDI knowledge acquisition, and we defer to the expert panel for specifications of the process. We also recommend that the standard set of DDIs be aligned with other national initiatives – both public and private (e.g., quality organizations) when creating quality metrics for healthcare organization quality assessments, including such organizations as the Pharmacy Quality Alliance and the National Quality Forum.

Key Question 2: What information should be included in a knowledgebase of standard DDIs

Based in part on recommendations by Floor-Schreudering *et al.*,[34] we formulated a list of information to be included, along with the interacting drug pairs, in a standard set of DDIs to optimally guide clinicians in mitigating or preventing harm. These include: (1) classification of seriousness; (2) clinical consequences; (3) frequency of harm and exposure; (4)

modifying factors; (5) interaction mechanism; (6) recommended action (with strength of recommendations); and (7) evidence (with quality ratings).

Classification (Seriousness Rating) and Meanings—The classification system for DDI must reflect and include an explanation of medical logic so the justification is intuitive to the end user (provider/pharmacist).[42] Information on the criteria used to classify drug pairs should be readily accessible. We recommend that classification terms (e.g., major, moderate, minor) be clearly defined, easily recognized, transparent, and simple. Many organizations and individuals refer to classification of DDIs by the "severity" of the interaction. We prefer the more precise term, "seriousness," defined as the extent to which an adverse reaction can or does cause harm.[43] Severity is more ambiguous and describes the intensity of an adverse reaction in an individual. For example, a headache may be severe but not serious. Seriousness, severity, and selected other terms related to DDIs have defined by others.[21]

The overall classification of an interaction should be driven by the seriousness and frequency (when available) of the potential clinical outcome, taking the clinical management recommendation(s) and strength of evidence into account. We recommend that decision support systems for DDIs use no more than three categories of seriousness. The rationale is to simplify and increase the consistency of these classification systems. The highest seriousness category should be for interruptive alerts for DDIs requiring clinician action. The middle category should be for DDIs requiring some form of clinician notification but that do not necessarily need to be an interruptive alert. The lowest category should be for clinically inconsequential DDIs that generally should not be included in notification systems.[24]

Clinical Consequences and Frequency—The potential adverse clinical consequences for the patient as a result of co-prescribing the interacting drugs should be clearly described. For example, simply stating that ciprofloxacin may increase the blood levels of theophylline is insufficient. Clinical effects of theophylline toxicity such as nausea, vomiting, cardiovascular instability, and seizures should be provided with the decision support information. Clinicians can make better therapeutic decisions for specific patients when the potential clinical consequences are clearly identified.[44]

When available, the frequency or incidence of adverse outcomes associated with a specific DDI should be stated in numbers (e.g., 1/1000). A verbal scale may be necessary, recognizing that numerical values are often unavailable and that estimated frequencies are often ranges of measures of central tendency (e.g., means) with wide variability from different studies.[45] One example is the standard frequency groupings for adverse effects used by the European Medicines Agency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).[46]

There are several impediments to identifying frequency estimates, such as underreporting, the nature of DDI evidence, and variability in the seriousness of adverse outcomes. Adverse reactions resulting from DDIs are likely to be underreported and the majority of clinical

evidence is currently derived from pharmacokinetic studies and case reports. Epidemiological evidence is infrequently published and, for most DDIs, evidence is sufficient to make only rough estimates of the incidence of adverse outcomes. In the near term, frequency is unlikely to be a commonly populated field, but clinicians should be informed that the rate of adverse events is unknown when not available.[34]

Modifying (Risk or Mitigating) Factors—The risk of harm associated with a DDI is a function of both seriousness and frequency of the event, combined with individual patient susceptibility. Risk factors increase patient susceptibility and mitigating factors decrease susceptibility. For example, risk factors for hyperkalemia among patients taking angiotensin-converting enzyme (ACE) inhibitors and potassium-sparing diuretics including renal impairment, diabetes, and elevated baseline potassium levels. Providing clinicians with information about factors that modify patient susceptibility is essential for assessing the risk of patient harm. For most DDIs, however, factors that modify the risk of an adverse outcome are often not known. Research shows that providing clinicians with alerts containing patient-specific risk factors can reduce the risk of injury.[47] Known modifying factors (such as patients' genetic information, ethnicity, concomitant diseases, etc.) should be included in DDI alerts, and when factors are not known, the lack of information should also be stated.

Interaction Mechanism—We recommend that clinically relevant information regarding interaction mechanisms, such as differentiating between pharmacokinetic and pharmacodynamics effects, should be included with the standard set of DDIs. This information may be useful to assess patient risk and identify reasonable therapeutic alternatives.

Recommended Actions in DDIs CDS—Providing a statement of possible harm without recommending a corresponding action is generally not an effective way to change clinician behavior.[48,49] Clinicians may resist an alert when an acceptable alternative is not offered.[49] We strongly recommend that CDS systems should provide actionable recommendations—that is, guidance on ways to mitigate or avoid the potential for harm, especially when a clinician's workflow is interrupted to display a potentially serious DDI. This could include a recommendation to closely monitor the patient while on the combination therapy. When the benefits of both medications outweigh the risks, it is critical to convey to the clinician strategies to minimize the potential for adverse outcomes, such as specific monitoring (e.g., vitals, labs, therapeutic drug monitoring) or dosage adjustments (e.g., 50% dose reduction). However, if the seriousness of the interaction dictates that the drugs should not be used together, the clinician must be presented with the option to discontinue one or both medications. As described previously, clear indications of the strength of the recommendations should accompany clinical advice.

Evidence—Providing access to the evidence is a critical component of weighing the risks and benefits. Unfortunately, many DDIs are based on limited evidence, such as a few case studies and perhaps pharmacokinetic evaluations. We recommend that DDI alerts should indicate the quality of evidence (with definitions), summarize the evidence briefly, and provide access to references from the primary literature when possible. Beyond the evidence

to substantiate the existence of a DDI, evidence ratings should also be provided when available for adverse effects, frequency, risk factors, and management strategies. In addition to ratings for the quality of evidence, links to primary sources should be accessible through the knowledgebase. Another workgroup associated with this project has recommended links to primary references through PMID numbers for PubMed or similar systems in other abstracting databases.[22]

Key Question 3: Can/should a list of contraindicated drug pairs be established?

It is important to recognize that there has been inconsistent use of the term "contraindicated" in various drug information sources. Contraindicated DDIs are those for which no situations have been identified where the benefit of the combination outweighs the risk.[3] Using this definition, there are *no* circumstances where an override is an acceptable action for contraindicated DDIs. In a review of contraindicated DDI alerts from a commercial knowledgebase, Hatton *et al.* suggested that most "contraindicated" drug pairs were not absolute contraindications and could be "downgraded."[14] For example, according to the sildenafil product labeling, sildenafil is contraindicated in patients regularly or intermittently using organic nitrates.[50] As such, many CDS systems produce DDI alerts identifying sildenafil and nitrates as contraindicated. However, evidence indicates that sildenafil and nitrates can be used intermittently with adequate separation of dosing (e.g., nitroglycerine may be considered 24 hours after sildenafil dosing) or with appropriate blood pressure monitoring).[51,52] Classifying an interaction as "contraindicated" should be done judiciously and perhaps infrequently, as only a small set of drug combinations are absolutely contraindicated. The Food and Drug Administration is aware of this issue and is making steps to limit the use of the term "contraindicated" or inferred contraindication in product labeling information. For example, rather than using the term "contraindicated," the labeling of ibrutinib states to "Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition," and provides specific instructions on how to manage the interaction.[53] Many times the contraindication may reflect avoidance of simultaneous administration, but this clarification needs to be included with the CDS notification. In other situations it may be appropriate to classify co-administration of two products as contraindicated based on extrapolation from other medications with similar pharmacologic properties (e.g., use of a novel antidepressant in combination with a monoamine oxidase inhibitor). Furthermore, a separate "contraindicated" classification should not be used for DDI alerts.

Key Question 4: How can DDI alerts be more intelligently filtered?

In an effort to reduce alert fatigue, many organizations have implemented local customization/revision of alerting rules.[42] However, implementation and modification of commercially developed CDS may result in unnecessary and/or error-inducing conditions that may need to be addressed at the organizational level.[54,55] There is lack of evidence on what approaches should be used when trying to filter alerts. Consequently, healthcare organizations should use an interprofessional committee, including physicians and pharmacists, to periodically review frequently overridden alerts and suggest safe and effective ways for either suppressing alerts of low value or changing their presentation format.[56] Individual users should be able to provide feedback to the committee about the

system at any point in the care process as part of a continuous improvement process. It is unclear whether individual clinicians should be allowed to turn off specific alerts they consider uninformative or whether entire classes of alerts could be safely suppressed for particular specialists, who may not need the same level of support as generalists.[42] An alternative approach would be to allow a prescriber to defer or forward an alert to a pharmacist for review during order verification when adjusting administration times can circumvent the DDI. We considered the question of whether organizations should identify a group of "expert" professionals that should be exempt from DDI notifications. However, there is no research to support that this approach protects patient safety.[57]

Keeping in mind the five "rights" for health IT medication safety (right information, right person, right CDS format, right channel, right time in workflow),[58] there are situations where DDI notification is repetitive or irrelevant. For example, in some systems, DDI alerts may be generated for refills or continuations of existing medications. Changes in dosing, strength, time of administration, and transfer between inpatient units can result in repetitive alerts that contribute to alert fatigue. Some experts advocate the ability to suppress alerts at the time of renewal of previously tolerated medication combinations for the same patient.[59,60] Patients with long-term use of certain medications may have demonstrated their capacity to tolerate them and suppressing alerts for refills might be an option in some circumstances.[61] We do not provide recommendations on this issue because of the paucity of evidence. We encourage organizations that design or modify CDS rules to evaluate outcomes and report to the medical community the effectiveness and safety of such modifications.

Filtering alerts by increasing the specificity of trigger rules may help to decrease irrelevant, interruptive messages.[62–64] More sophisticated rules need to be developed to enable intelligent alerting. Ideally, DDI alerts should be patient-specific, taking into account age, gender, genetics, body weight, allergies, drug serum levels, renal function, comorbidity, and other mitigating factors.[65] Table 1 provides an overview of situations where a particular DDI alert may be intelligently ignored in a specific patient. We recognize the challenges posed by incorporating mitigating factors into DDI alerts and that there is often insufficient clinical evidence to improve patient-specificity for many interactions. As CDS systems become more sophisticated, developers are encouraged to take context into account when designing alerts. Given the current state of the evidence, we do not support indiscriminately "turning off" alerts,[55] and recommend that modifications to DDI alerts be done cautiously, with careful evaluation to ensure that patient safety is not compromised. Furthermore, suggesting strategies to actively monitor for signs of harm for patients on concomitant therapies that may result in a DDI should be incorporated into CDS systems.

DISCUSSION

The purpose of this paper is to present recommendations from a national workgroup on approaches that should be undertaken to improve CDS for DDIs. We believe that implementing these recommendations will provide substantive improvements to current systems. Foremost, employing a systematic process with graded recommendations and full transparency for a nationally vetted, standard set of clinically relevant DDIs will build trust among clinicians and foster collaboration among healthcare organizations and IT

vendors.[25,26,28,42] The threat of liability often dominates the decision to list a drug pair as a DDI, even when evidence or even plausibility is lacking. We believe a systematic process will help mitigate liability risk and may reduce alert burden and ultimately improve patient safety.[29,30] Presently, there is no well-defined, broadly accepted standard for grading the quality of a body of evidence for a DDI and for providing strengths of recommendations for patient risk management strategies.[23,24,29,30,34] In addition, research is needed to develop new approaches that will further allow further refinement of DDIs such as consideration of patient characteristics when considering if or how to fire a DDI. Filling these unmet needs is an important goal to provide widely accepted and consistent DDI alerts.

Creating and maintaining a list of DDIs is a resource-intensive, time-consuming, and continuous process, not a one-time activity. The task a central organizer/convener will face to create and maintain the proposed knowledgebase and standard set of DDIs is enormous. Much oversight will be required to coordinate evidence evaluation and continual updates. Decisions should be subject to periodic review along with regular review of underlying methods to remain current with evolving scientific knowledge. Support and buy-in (or adoption) from the major stakeholders will be essential to the success of the endeavor. To minimize issues of bias, we recommend that public funding take the lead in supporting these administrative efforts. The standard set of DDIs should be aligned with other national initiatives – both public and private (e.g., quality organizations) when creating quality metrics for healthcare organizations.

Given the cost and difficulty of securing continued public funding, the primary challenge to implementing our recommended process is sustainability. An innovative public-private partnership is needed with endorsement and support from all relevant stakeholders, including government agencies, professional organizations, drug knowledgebase and compendia editors, and healthcare systems. Currently, there is no process in place that brings the collective knowledge of DDI experts, including knowledgebase/compendia editors, together to reach consensus on those interactions that should be included in warning systems. Collaboration and pooling of limited resources will be necessary to maintain a current standard set of DDIs to protect patient safety.

Much work is needed to provide evidence-based recommendations for other changes to implementing DDI alerts. Table 2 lists areas of future research that would support modifications to DDI alerting systems. Although filtering of alerts by provider type is often suggested in the literature, we recommend that modifications to systems be evaluated prior to implementation to ensure that patient safety is not compromised.

CONCLUSION

Our purpose was to improve the content of DDI alerts. To this end, our primary recommendation is to establish an expert panel with a centralized organizer/convener to develop and maintain a standard set of DDIs for CDS in the United States. The process should be evidence-driven, transparent, and systematic, with feedback from multiple stakeholders for continuous improvement. The scope of the expert panel's work should be carefully managed to assure the process is sustainable. Support for research to improve DDI

alerting in the future is also needed. We anticipate that our recommendations can lead to consistent and clinically relevant content for interruptive DDI, and thus reduce alert fatigue and improve patient safety.

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REFERENCES

1. Preventing Medication Errors: Quality Chasm Series. 2006 [Accessed April 22, 2014] http://www.iom.edu/Reports/2006/Preventing-Medication-Errors-Quality-Chasm-Series.aspx.
2. Chaffee BW, Zimmerman CR. Developing and implementing clinical decision support for use in a computerized prescriber-order-entry system. Am J Health Syst Pharm. 2010; 67(5):391–400. [PubMed: 20172991]
3. Hansten PD, Horn JR, Hazlet TK. ORCA: OpeRational ClassificAtion of drug interactions. J Am Pharm Assoc (Wash). 2001; 41(2):161–165. [PubMed: 11297327]
4. CMS. [Accessed 01/09/2013] Eligible Professional Meaningful Use Core Measures: Measure 2 of 15. Centers for Medicare and Medicaid Services. 2010. http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/downloads/2_Drug_Interaction_ChecksEP.pdf
5. Blumenthal D, Tavenner M. The "meaningful use" regulation for electronic health records. N Engl J Med. 2010; 363(6):501–504. [PubMed: 20647183]
6. Kesselheim AS, Cresswell K, Phansalkar S, Bates DW, Sheikh A. Clinical decision support systems could be modified to reduce 'alert fatigue' while still minimizing the risk of litigation. Health Aff (Millwood). 2011; 30(12):2310–2317. [PubMed: 22147858]
7. Jankel CA, Martin BC. Evaluation of six computerized drug interaction screening programs. Am J Hosp Pharm. 1992; 49(6):1430–1435. [PubMed: 1529984]
8. Cavuto NJ, Woosley RL, Sale M. Pharmacies and prevention of potentially fatal drug interactions. JAMA. 1996; 275(14):1086–1087. [PubMed: 8601923]
9. Hazlet TK, Lee TA, Hansten PD, Horn JR. Performance of community pharmacy drug interaction software. J Am Pharm Assoc (Wash). 2001; 41(2):200–204. [PubMed: 11297332]
10. Smith WD, Hatton RC, Fann AL, Baz MA, Kaplan B. Evaluation of drug interaction software to identify alerts for transplant medications. Ann Pharmacother. 2005; 39(1):45–50. [PubMed: 15598964]
11. Abarca J, Colon LR, Wang VS, Malone DC, Murphy JE, Armstrong EP. Evaluation of the performance of drug-drug interaction screening software in community and hospital pharmacies. J Manag Care Pharm. 2006; 12(5):383–389. [PubMed: 16792445]
12. Saverno KR, Hines LE, Warholak TL, et al. Ability of pharmacy clinical decision-support software to alert users about clinically important drug-drug interactions. J Am Med Inform Assoc. 2011; 18(1):32–37. [PubMed: 21131607]
13. Metzger J, Welebob E, Bates DW, Lipsitz S, Classen DC. Mixed results in the safety performance of computerized physician order entry. Health Aff (Millwood). 2010; 29(4):655–663. [PubMed: 20368595]

14. Hatton RC, Rosenberg AF, Morris CT, McKelvey RP, Lewis JR. Evaluation of contraindicated drug-drug interaction alerts in a hospital setting. Ann Pharmacother. 2011; 45(3):297–308. [PubMed: 21386026]
15. Shah NR, Seger AC, Seger DL, et al. Improving acceptance of computerized prescribing alerts in ambulatory care. J Am Med Inform Assoc. 2006; 13(1):5–11. [PubMed: 16221941]
16. Murphy JE, Forrey RA, Desiraju U. Community pharmacists' responses to drug-drug interaction alerts. Am J Health Syst Pharm. 2004; 61(14):1484–1487. [PubMed: 15332698]
17. Weingart SN, Simchowitz B, Shiman L, et al. Clinicians' assessments of electronic medication safety alerts in ambulatory care. Arch Intern Med. 2009; 169(17):1627–1632. [PubMed: 19786683]
18. van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc. 2006; 13(2):138–147. [PubMed: 16357358]
19. Isaac T, Weissman JS, Davis RB, et al. Overrides of medication alerts in ambulatory care. Arch Intern Med. 2009; 169(3):305–311. [PubMed: 19204222]
20. Bryant AD, Fletcher GS, Payne TH. Drug interaction alert override rates in the Meaningful Use era. No evidence of progress. Applied Clinical Informatics. 2014; 5(3):802–813. [PubMed: 25298818]
21. Scheife RTHL, Boyce RD, Chung SP, Momper JD, Sommer CD, Abernethy DR, Horn JR, Sklar SJ, Wong SK, Jones G, Brown ML, Grizzle AJ, Comes S, Wilkins TL, Borst C, Wittie MA, Malone DC. Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical decision support. Drug Saf. 2015 Feb; 38(2):197–206. [PubMed: 25556085]
22. Payne THHL, Chan RC, Hartman S, Kapusnik-Uner J, Russ AL, Chaffee BW, Hartman C, Tamis V, Galbreth B, Glassman PA, Phansalkar S, van der Sijs H, Gephart SM, Mann G, Strasberg HR, Grizzle AJ, Brown M, Kuperman GJ, Steiner C, Sullins A, Ryan H, Wittie MA, Malone DC. Recommendations to Improve the Usability of Drug-Drug Interaction Clinical Decision Support Alerts. J Am Med Inform Assoc. 2015 (in press).
23. Phansalkar S, Desai AA, Bell D, et al. High-priority drug-drug interactions for use in electronic health records. J Am Med Inform Assoc. 2012; 19(5):735–743. [PubMed: 22539083]
24. Phansalkar S, van der Sijs H, Tucker AD, et al. Drug-drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records. J Am Med Inform Assoc. 2013; 20(3):489–493. [PubMed: 23011124]
25. Sox HC. Assessing the trustworthiness of the guideline for management of high blood pressure in adults. JAMA. 2014; 311(5):472–474. [PubMed: 24352688]
26. Clinical Practice Guidelines We Can Trust. 2011 [Accessed April 22, 2014] http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx.
27. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336(7650):924–926. [PubMed: 18436948]
28. Marriott J, Stehlik P. A critical analysis of the methods used to develop explicit clinical criteria for use in older people. Age Ageing. 2012; 41(4):441–450. [PubMed: 22711452]
29. Ridgeley MS, Greenberg MD. Too many alerts, too much liability: Sorting through the malpractice implications of drug-drug interaction clinical decision support. Saint Louis University Journal of Health Law and Policy. 2012; 5(257):257–296.
30. Hoffman S, Podgurski A. Drug-Drug Interaction Alerts: Emphasizing The Evidence. Saint Louis University Journal of Health Law & Policy. 2012; 5(2):297–309.
31. Weingart SN, Seger AC, Feola N, Heffernan J, Schiff G, Isaac T. Electronic drug interaction alerts in ambulatory care: the value and acceptance of high-value alerts in US medical practices as assessed by an expert clinical panel. Drug Saf. 2011; 34(7):587–593. [PubMed: 21663334]
32. The University of Liverpool. HIV-Drug Interactions. [Accessed December 1, 2014] http://www.hiv-druginteractions.org.
33. The University of Liverpool. HEP-Drug Interactions. [Accessed December 1, 2014] http://www.hep-druginteractions.org/.
34. Floor-Schreudering A, Geerts AF, Aronson JK, Bouvy ML, Ferner RE, De Smet PA. Checklist for standardized reporting of drug-drug interaction management guidelines. Eur J Clin Pharmacol. 2014; 70(3):313–318. [PubMed: 24306496]

35. Khoo, S.; Gibbons, S.; Seden, K.; Black, D. [Accessed April 22, 2014] Systematic review: Drug-drug Interactions between Antiretrovirals and medications used to treat TB, Malaria, Hepatitis B&C and opioid dependence. 2014. http://www.who.int/hiv/topics/treatment/drug_drug_interactions_review.pdf
36. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26.336:924–926. [PubMed: 18436948]
37. Grade Working Group. [Accessed July 28, 2014] http://www.gradeworkinggroup.org/society/index.htm.
38. Hines LE, Malone DC, Murphy JE. Recommendations for generating, evaluating, and implementing drug-drug interaction evidence. Pharmacotherapy. 2012; 32(4):304–313. [PubMed: 22461120]
39. Schunemann HJ, Best D, Vist G, Oxman AD. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. CMAJ. 2003; 169(7):677–680. [PubMed: 14517128]
40. Wright A, Sittig DF, Ash JS, et al. Governance for clinical decision support: case studies and recommended practices from leading institutions. J Am Med Inform Assoc. 2011; 18(2):187–194. [PubMed: 21252052]
41. van Roon EN, Flikweert S, le Comte M, et al. Clinical relevance of drug-drug interactions : a structured assessment procedure. Drug Saf. 2005; 28(12):1131–1139. [PubMed: 16329715]
42. Horsky J, Schiff GD, Johnston D, Mercincavage L, Bell D, Middleton B. Interface design principles for usable decision support: a targeted review of best practices for clinical prescribing interventions. J Biomed Inform. 2012; 45(6):1202–1216. [PubMed: 22995208]
43. Talbot, JCC.; Aronson, JK.; Stephens, MDB. Stephens' detection and evaluation of adverse drug reactions : principles and practice. 6th. Chichester, West Sussex, UK: John Wiley & Sons; 2011.
44. Ashworth M. Re: GPs' views on computerized drug interaction alerts. J Clin Pharm Ther. 2002; 27(5):311–312. [PubMed: 12383130]
45. Calman KC. Cancer: science and society and the communication of risk. BMJ. 1996; 313(7060): 799–802. [PubMed: 8842078]
46. A Guideline on Summary of Product Characteristics. European Commission Enterprise and Industry Directorate-General. 2009 Sep. http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf.
47. Tamblyn R, Eguale T, Buckeridge DL, et al. The effectiveness of a new generation of computerized drug alerts in reducing the risk of injury from drug side effects: a cluster randomized trial. J Am Med Inform Assoc. 2012; 19(4):635–643. [PubMed: 22246963]
48. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ. 2005; 330(7494):765. [PubMed: 15767266]
49. Bates DW, Kuperman GJ, Wang S, et al. Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. J Am Med Inform Assoc. 2003; 10(6):523–530. [PubMed: 12925543]
50. Viagra [package insert]. New York, NY: Pfizer Laboratories Div Pfizer Inc; 2014.
51. Werns SW. Are nitrates safe in patients who use sildenafil? Maybe. Crit Care Med. 2007; 35(8): 1988–1990. [PubMed: 17667250]
52. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation. 2007; 116(7):e148–304. [PubMed: 17679616]

53. DailyMed. [Accessed May 5, 2015] U.S. National Library of Medicine. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0dfd0279-ff17-4ea9-89be-9803c71bab44
54. Miller AM, Boro MS, Korman NE, Davoren JB. Provider and pharmacist responses to warfarin drug-drug interaction alerts: a study of healthcare downstream of CPOE alerts. J Am Med Inform Assoc. 2011; 18(Suppl 1):i45–i50. [PubMed: 22037888]
55. van der Sijs H, Aarts J, van Gelder T, Berg M, Vulto A. Turning off frequently overridden drug alerts: limited opportunities for doing it safely. J Am Med Inform Assoc. 2008; 15(4):439–448. [PubMed: 18436915]
56. Gardner RM, Evans RS. Using computer technology to detect, measure, and prevent adverse drug events. J Am Med Inform Assoc. 2004; 11(6):535–536. [PubMed: 15317740]
57. Riedmann D, Jung M, Hackl WO, Stuhlinger W, van der Sijs H, Ammenwerth E. Development of a context model to prioritize drug safety alerts in CPOE systems. BMC Med Inform Decis Mak. 2011; 11:35. [PubMed: 21612623]
58. Teich JM, Osheroff JA, Pifer EA, Sittig DF, Jenders RA, Panel CER. Clinical decision support in electronic prescribing: recommendations and an action plan: report of the joint clinical decision support workgroup. J Am Med Inform Assoc. 2005; 12(4):365–376. [PubMed: 15802474]
59. Kuperman GJ, Bobb A, Payne TH, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc. 2007; 14(1):29–40. [PubMed: 17068355]
60. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med. 2003; 163(21):2625–2631. [PubMed: 14638563]
61. Tamblyn R, Huang A, Taylor L, et al. A randomized trial of the effectiveness of on-demand versus computer-triggered drug decision support in primary care. J Am Med Inform Assoc. 2008; 15(4): 430–438. [PubMed: 18436904]
62. Seidling HM, Klein U, Schaier M, et al. What, if all alerts were specific - Estimating the potential impact on drug interaction alert burden. Int J Med Inform. 2014; 83(4):285–291. [PubMed: 24484781]
63. Ammenwerth E, Hackl WO, Riedmann D, Jung M. Contextualization of automatic alerts during electronic prescription: researchers' and users' opinions on useful context factors. Stud Health Technol Inform. 2011; 169:920–924. [PubMed: 21893880]
64. Duke JD, Bolchini D. A successful model and visual design for creating context-aware drug-drug interaction alerts. AMIA Annu Symp Proc. 2011; 2011:339–348. [PubMed: 22195086]
65. van den Bemt PM, Egberts AC, Lenderink AW, et al. Risk factors for the development of adverse drug events in hospitalized patients. Pharm World Sci. 2000; 22(2):62–66. [PubMed: 10849925]
66. Ko Y, Malone DC, D'Agostino JV, et al. Potential determinants of prescribers' drug-drug interaction knowledge. Res Social Adm Pharm. 2008; 4(4):355–366. [PubMed: 19064242]

Key Points

A national panel should be established to evaluate drug-drug interaction evidence and make recommendations as to what interactions should be included in clinical decision support systems.

The term “contraindicated” should be reserved for those drug pairs where co-administration should not be permitted under any circumstances.

More research is needed to determine if filtering of drug interaction alerts can be done safely.

Figure 1.

Schematic of Transparent and Systematic Process to Develop and Maintain a Standard Set of DDIs for CDS Alerts

Table 1

Examples of Mitigating Factors Allowing for Intelligent Filtering of DDI Alerts

Mitigating Factor	Explanation
Drug Dose/Duration	• Dose and/or duration of object or precipitant drug may be insufficient to result in an adverse outcome. • A few doses of a NSAID during ACE inhibitor antihypertensive therapy are unlikely to result in clinically important increased blood pressure.
Timing of Administration	• With some GI absorption interactions, administering the affected drug (e.g., ciprofloxacin) at least 2 hours before or 4-6 hours after the binding agent (e.g., ferrous sulfate) can often circumvent the interaction.
Route of Administration	• Some routes of administration may avoid the interaction. • With some GI absorption interactions, administering the affected drug parenterally (e.g., ciprofloxacin) may circumvent the interaction (e.g., with ferrous sulfate). • Topically applied medications (e.g., erythromycin ophthalmic ointment) may not achieve sufficient systemic concentrations to interact. • Caution is needed for drugs with significant absorption when administered by non-systemic routes (e.g., inhaled fluticasone with CYP3A4 inhibitors can lead to hypothalamic-pituitary-adrenal axis suppression).
Sequence of Therapy	• The sequence (order) of starting therapies can influence the risk of a DDI. • When an object drug is given chronically and is carefully titrated (e.g., warfarin), adding a precipitant drug (e.g., amiodarone) requires careful monitoring. • Conversely, the likelihood of a DDI is usually small when starting an object drug with careful titration (e.g., warfarin) for a patient already on chronic therapy with the precipitant drug (e.g., amiodarone).
Pharmacogenomics	• Pharmacogenomics can influence the risk of a DDI. • Patients who are genotyped to be poor metabolizers of CYP2D6 are unlikely to have a clinically significant interaction between venlafaxine and CYP2D6 inhibitor (e.g., diphenhydramine).
Indication for drug	• In some cases, drugs with potentially serious DDIs may be purposely and safely co-prescribed by experienced clinicians. • Starting allopurinol in a patient on azathioprine can result in potentially fatal bone marrow suppression. • Conversely, allopurinol and azathioprine can be beneficial for inflammatory bowel disease when carefully managed and monitored by a gastroenterologist.

ACE = angiotensin-converting enzyme; CYP = cytochrome P450 enzyme; DDI = drug-drug interaction GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug

Table 2

Recommendations for Future Research to Improve DDI Alert Content

Topic	Comments and Recommendations
Clinical Consequences of DDIs and Frequencies	• Conduct population-based research to more clearly delineate the nature and frequency of DDIs and adverse outcomes associated with DDIs.
Modifying (Risk or Mitigating) Factors	• Identify modifying factors that are associated with lower or higher risk of harm.
Filtering Alerts	• Identify methods to safely reduce repetitive and less relevant alerts. • Demonstrate the safety of suppressing alerts at the time of renewal of previously tolerated medication combinations for the same patient. • Evaluate of the impact of filtering DDI alerts based on provider type, years of experience, specialty, or location (e.g., unit, ward, or facility), etc. • Determine if alerts can be safely suppressed for particular medical specialties (e.g., anesthesiology) or in closely managed patient care settings—such as the surgical suite.[66]
Seriousness Categories	• Determine the optimal names and quantity of seriousness categories.