

Drug–drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records

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ABSTRACT

Objective Alert fatigue represents a common problem associated with the use of clinical decision support systems in electronic health records (EHR). This problem is particularly profound with drug–drug interaction (DDI) alerts for which studies have reported override rates of approximately 90%. The objective of this study is to report consensus-based recommendations of an expert panel on DDI that can be safely made non-interruptive to the provider's workflow, in EHR, in an attempt to reduce alert fatigue.

Methods We utilized an expert panel process to rate the interactions. Panelists had expertise in medicine, pharmacy, pharmacology and clinical informatics, and represented both academic institutions and vendors of medication knowledge bases and EHR. In addition, representatives from the US Food and Drug Administration and the American Society of Health-System Pharmacy contributed to the discussions.

Results Recommendations and considerations of the panel resulted in the creation of a list of 33 class-based low-priority DDI that do not warrant being interruptive alerts in EHR. In one institution, these accounted for 36% of the interactions displayed.

Discussion Development and customization of the content of medication knowledge bases that drive DDI alerting represents a resource-intensive task. Creation of a standardized list of low-priority DDI may help reduce alert fatigue across EHR.

Conclusions Future efforts might include the development of a consortium to maintain this list over time. Such a list could also be used in conjunction with financial incentives tied to its adoption in EHR.

INTRODUCTION

Medication-related clinical decision support (CDS) when implemented in electronic health records (EHR) has the potential to reduce the frequency of preventable adverse drug events.^{1–2} CDS implemented at the point of prescribing can change provider behavior resulting in improved patient safety³ and can also facilitate provider workflow.⁴ Despite these benefits, medication-related CDS alerts are often ignored and several studies cite very high override rates ranging between 49% and 96%,^{5–7} with a rate of 90% for drug–drug interaction (DDI) alerts specifically.⁵ Kuperman *et al*⁸ cited lack of content specificity with respect to DDI as a particular reason for the high rates of DDI overrides.

While tailoring knowledge bases is one option to improve DDI content specificity, it is resource intensive and thus not feasible for most

organizations.⁸ To help harness the benefits of medication-related CDS in EHR and improve the acceptance of medication-related CDS alerts, the Office of the National Coordinator sponsored an effort to decrease the burden of alert fatigue.⁹ Peterson and Bates¹⁰ described alert fatigue as the mental state resulting from receiving too many alerts that consume time and mental energy, which can cause important alerts to be ignored along with clinically unimportant ones. Consequently, alert fatigue may compromise patient safety by decreasing the potential safety benefits of implementing CDS in EHR. In a previous study, we described a set of high-priority DDI that should always be included in medication-related CDS knowledge bases for alerting providers. The set of critical DDI and the process employed in identifying them is described elsewhere.¹¹

The list of high-priority DDI consists of a small list of interactions that meet the stringent criteria of those drugs that should never be prescribed together, and DDI alerting should not be restricted to just that small list. Another approach to the problem of DDI over-alerting is to identify DDI that account for a significant fraction of all alerts, which might be safely made non-interruptive by modifying their severity level or how they are implemented. In the context of this paper, we have used the term 'non-interruptive alerts' to mean those alerts that do not interrupt the provider's workflow, which consequently implies that these alerts do not require the user to provide a response when these are generated. In this study, we sought to identify alerts that result from DDI that occur often yet are nearly always overridden, suggesting that they can safely be made non-interruptive to a providers' workflow in an attempt to reduce alert fatigue. Our goal in employing a two-pronged approach was to be able to reduce the total number of alerts shown to providers to increase clinician attentiveness to clinically significant alerts, thereby improving patient safety. The aim of this study is to describe the process used in identifying non-critical DDI that can be safely made non-interruptive to a providers' workflow when using an EHR system.

METHODS

In order to conduct this analysis, we obtained the alert logs from one academic medical center, which employs a commercially developed EHR with a vendor developed medication knowledge base. The alert logs spanned a 6-month time period from 1 June 2010 to 30 November 2010 and spanned

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all levels of severity. At this institution, alerts of all severities are generated in an interruptive manner and any alert can be overridden without the provider having to document a reason.

From the alert logs we normalized the data to identify the DDI pairs, and these interacting pairs were further normalized in order to represent them as drug–class and class–class interactions. The reason for the second stage of normalization was to identify class-based interactions, in which multiple members within a class would display the same interaction characteristics. These interactions occur as a result of the concurrent administration of drugs that have the same or opposing pharmacologic actions and result in a change in the sensitivity or the responsiveness to one drug in the presence of the other drug. For example, multiple agents belonging to the class of non-steroidal anti-inflammatory drugs (NSAID) may inhibit the antihypertensive effect of drugs in the class of ACE inhibitors (captopril, enalapril, lisinopril) and can result in hyperkalemia especially in patients with compromised renal function. Therefore, instead of individual agents we would represent this interaction to occur between the classes of NSAID and ACE inhibitors.

We set the threshold for inclusion to those interactions with override rates greater than 90% to identify those alerts that had a high rate of override and would thus have a large contribution to alert fatigue. The final interactions were presented to a panel of experts who were chosen on the basis of their knowledge and expertise in the area of medication-related decision support, especially DDI in the use of medication knowledge bases for EHR systems. The panel included 11 experts with broad expertise in the domain of medication-related decision support from the perspective of the clinician end-user, pharmacist, pharmacologists, and clinical informaticists. We invited panelists with expertise in the development, implementation, and maintenance of medication-related CDS content at academic medical centers with either their proprietary medication knowledge bases or using a commercial knowledge base. Panelists also represented medication knowledge base and EHR vendors. In addition, we invited experts from regulatory bodies such as the US Food and Drug Administration and professional societies with an interest in this domain such as the American Society of Health-System Pharmacy to participate on the panel.

Each panelist was provided with the list of interactions along with information on the mechanism of the interaction, severity level assigned in knowledge bases, such as First Databank (FDB) (San Francisco, California, USA), Micromedex (New York, New York, USA), Cerner Multum (Denver, Colorado, USA), the type of interaction (pharmacodynamic/pharmacokinetic interaction), predisposing risk factors, and management options to reduce the severity of interaction, in order to assess the severity of the interaction. Each panelist was asked to assess whether the interaction could be safely made non-interruptive or not. In addition, panelists were asked to evaluate any exceptions to memberships of drug classes based on literature evidence. A consensus meeting was held by conference call to discuss panelists' ratings on the interaction. The meeting was moderated by an expert in the domain of medication-related decision support (DWB). Following the call, experts were asked to submit their final ratings. These ratings were analyzed for consensus; those interactions that did not have a clear vote were re-rated by the panelists by providing them with additional literature evidence and comments from other panelists to help ascertain their decision. The final ratings helped determine the set of low-priority interactions that can be safely generated as non-interruptive alerts in EHR.

RESULTS

The alert logs consisted of 4077 DDI pairs, which were responsible for a total of 158 794 alerts being fired in the 6-month time period. These interacting pairs were normalized to represent a final list of 1339 drug–class and class–class interactions. Excluding interactions that accounted for less than 0.2% of alerts in the dataset and those for which the override rates were less than 90% produced a list of the 114 most frequently fired DDI alert pairs. From this list, we discussed the top 50 most frequently occurring DDI with the expert panel based on the number of alerts that these DDI generated. Cumulatively, these accounted for half the alerts that were shown to providers and they had an average override rate of between 95.1% and 99.3%.

The panel was asked to rate whether an interaction could be safely made non-interruptive. Of the 50 interactions that were assessed, one DDI, between iron salts and proton pump inhibitors, was found to occur twice and was counted only once to bring the total of reviewed interactions to 49. Votes needed to be recast for six interactions in which a clear consensus could not be achieved between panelists; these were interactions between ACE inhibitors and salicylates, niacin and statins, ACE inhibitors and NSAID, beta-adrenergic blockers and serotonin reuptake blockers, narcotic analgesics and serotonin reuptake blockers and between serotonin reuptake blockers and NSAID. Following the recast of votes, two of the interactions between narcotic analgesics and serotonin reuptake inhibitors and between serotonin reuptake blockers and NSAID were considered significant enough to warrant interruptive alerting, while the rest were rated as safe for non-interruptive alerting. In all, the panel achieved consensus that 16 of the interactions should remain interruptive in nature and that 33 could safely be changed to non-interruptive alerts. These 33 class-based interactions accounted for over a third, or specifically 36.21%, of alerts generated in the EHR. Table 1 describes the list of low-priority DDI that the panel assessed as safe for non-interruptive alerting in EHR. Table 2 describes the remaining DDI from the initial list that were assessed by the panel but determined to be important enough to warrant an interruptive alert.

DISCUSSION

We implemented a consensus-based process that resulted in the development of a list of DDI that can be safely generated as non-interruptive alerts, with the aim to decrease alert fatigue.

We found that a very small number of alerts accounted for a large proportion of interruptive alerting. This is illustrated in supplementary figure S1 (available online only) in which 50 interactions contribute to a little more than half of the alerts that are seen by the providers (51%). In addition, by evaluating only those alerts that met our stringent criteria in terms of frequent occurrence and those alerts that are often overridden, we were able to identify the DDI that would make the most impact on alert fatigue. If the 33 DDI identified here were safely made non-interruptive one could potentially reduce alert volume by about a third. This is an estimation based on what was observed from one knowledge base at one academic institution and these findings need to be further validated to ascertain the actual impact on alert fatigue.

In comparison to previous studies, such as the one conducted by Van der Sijs *et al.*,¹² in which individual prescribing physicians were interviewed regarding their preferences for turning off frequently overridden alerts, this study utilized a consensus-based approach among an international panel of experts in

Table 1 List of low-priority DDI that the panel assessed as safe to suppress from interruptive alerting in EHR

Object drug/class	Precipitant drug/class
ACE inhibitors	Salicylates
Niacin	Statins
β-Adrenergic blockers	Serotonin reuptake blockers
Iron salts	Proton pump inhibitors
Thiazide-type diuretics	ACE inhibitors
Thyroid hormones	Calcium salts
Thyroid hormones	Statins
Thiazide-type diuretics	NSAID
β-Adrenergic blockers	Thyroid hormones
Macrolide immunosuppressives	Corticosteroids
Antacids	Corticosteroids (oral)
Bisphosphonates	Calcium salts
Vitamin B12	Omeprazole
Folic acid	Methotrexate
Sulfonylureas	ACE inhibitors
Iron salts	Thyroid hormones
Anticoagulants	Corticosteroids
Anticoagulants	Acetaminophen
Antacids	Iron salts (oral)
Anticoagulants	Proton pump inhibitors
Proton pump inhibitors	Imidazoles
β-Adrenergic blockers	Calcium salts (oral)
ACE inhibitors	Angiotensin II receptor antagonists
Anticoagulants	Statins
Omeprazole	Benzodiazepines
Anticoagulants	Vitamin E
Zinc salts (oral)	Quinolones (oral)
NSAIDs	β-Adrenergic blockers
Clopidogrel	Salicylates
Oral contraceptives	Corticosteroids
β-Adrenergic blockers	Nifedipine and derivatives
Corticosteroids/corticotropin	Anticholinesterases
ACE inhibitors	NSAID

DDI, drug–drug interaction; EHR, electronic health record; NSAID, non-steroidal anti-inflammatory drug.

medication-related CDS representing diverse perspectives. We do not recommend completely turning off the low-priority alerts identified here but instead presenting them non-interruptively, which may help reduce the problem of alert fatigue by decreasing the interruptions in a provider's workflow. Many commercial medication knowledge bases are over-inclusive as a result of the fear of liability considerations.¹³ Knowledge base vendors are wary of legal consequences if they do not include every potential DDI, and EHR vendors are cautious of turning off alerts for drug combinations mentioned in the literature as potentially harmful. Kesselheim *et al*¹³ assessed product liability principles and described how medication knowledge bases could be tailored to decrease alert fatigue without imparting a high risk of litigation to stakeholders.

The majority of DDI assessed by the panel were not present in more than one of the commonly used commercial knowledge bases. This may suggest that these DDI indeed have low severity levels and can possibly be safely made non-interruptive. It also further validates the fact that knowledge bases differ considerably in their content, and this issue has been described previously in the literature.^{14–18} A uniform standard for rating DDI would be helpful as different methods exist and are used

Table 2 DDI assessed by the panel to warrant interruptive alerting

Object drug/class	Precipitant drug/class
Calcium salts	Quinolones (oral)
Corticosteroids	Quinolones
Narcotic analgesics	Serotonin reuptake blocker
Serotonin reuptake blockers	NSAID
ACE inhibitors	Potassium preparations
Serotonin reuptake blockers	Salicylates
Diltiazem	Statins
Azole antifungals	Corticosteroids
Insulin	β-Adrenergic blockers (non-selective)
Narcotic analgesics	Diltiazem
Potassium preparations	Angiotensin antagonists
Magnesium salts (oral)	Quinolones (oral)
Fibric acid derivatives	Statins
Potassium preparations	Potassium-sparing diuretics
Erythromycin	HIV protease inhibitors
Colchicine	Statins

DDI, drug–drug interaction; NSAID, non-steroidal anti-inflammatory drug.

variably by different knowledge base vendors.^{19–20} In addition, there is variation in the interpretation of what constitutes a DDI, for example, panel members differed in their interpretation of whether the interaction between ACE inhibitors and angiotensin II receptor blockers should be considered a DDI or a therapeutic duplication caused by the underlying mechanism of inhibition of the renin–angiotensin–aldosterone system. Following the discussion, this interaction was included in the list of low-priority DDI that can be safely made non-interruptive. The current study employed a pragmatic approach by utilizing alert logs to identify those DDI that are frequently overridden as a starting point for the pre-selection of low-priority DDI. A high override rate for an alert is a proxy measure that the alert may be considered clinically irrelevant or not particularly helpful at the time the alert is presented in most patient contexts. However, one should keep in mind that overriding an alert is often clinically appropriate, and providers must make their decisions after carefully weighing risks against benefits, and considering other precautions such as increased monitoring.⁵ In fact, Weingart *et al*²¹ surveyed providers regarding the usefulness of CDS alerts, and found that 63% of the providers took an action other than discontinuing or modifying a prescription in response to an alert. Future studies should use stronger empirical data, when available, to support the impact of alerts, in addition to the use of override rates.

The list discussed here consists of several categories of DDI, as described in table 1. A large number of these are time-dependent interactions that occur due to co-administration within a 2–4 h interval. Expert opinion was to make the alerts for these drug combinations non-interruptive during order entry. Options to prevent concomitant administration of these combinations are changing drug administration times by the pharmacy, or alerting nurses during electronic drug administration registration.²² Another group of alerts to be made non-interruptive consists of drug combinations that may result in decreased antihypertensive effects that present after approximately 2 weeks of combined use. This does not warrant interruptive alerting during order entry but merits a less interruptive warning type if the concurrent use exceeds a time period of 2 weeks.

Anticoagulants are especially high risk for DDI and for this reason the Institute for Safe Medication Practices has assigned a high alert status to this class of drugs.²³ Many antibiotics and analgesics when taken in combination with warfarin are known to elevate the international normalized ratio and increase the risk of a bleeding event. The panel noted that in most scenarios the provider would continue to use these drugs in combination but would monitor the patient more carefully. Several DDI with anticoagulants are thus included on the list of alerts that can be safely made non-interruptive. Although the individual DDI were combined to drug-class and class-class interactions, several members within a class can be excluded from the alert based on their specific metabolic profile. An example is the combination of thyroid hormones and statins resulting in increased levothyroxine metabolism, which may only be relevant for atorvastatin and simvastatin and not for all statins that may exhibit an alternative metabolic profile. A class-based drug interaction profile may be easier for maintenance of the knowledge base but assessment by drug member is necessary in order to achieve higher specificity and prevent over-alerting.

Another measure to increase specificity is to include patient parameters, such as serum levels of specific biomarkers for consideration in clinical rules in the EHR.²⁴ Although this is a successful way to improve specificity it is time consuming to develop and implement.²⁵ Another barrier in the implementation of such rules may be the inability of current medication knowledge bases to utilize clinical parameters as expressed in the EHR. Lack of standardization of the terminologies utilized by EHR inhibits the creation of such rules and further work is needed to allow the standardization of terminologies for the expression of comorbidities and laboratory values in EHR and their use by medication knowledge bases for CDS.

The strength of the present study is that a pragmatic approach was undertaken rather than a comprehensive literature review, which is resource intensive and may not actually result in the identification of 'heavy-hitters' in terms of DDI alerts contributing to alert fatigue. By employing a diverse panel of international experts that represented both commercial vendors of medication knowledge bases and EHR, regulatory agencies such as the US Food and Drug Administration, professional societies such as the American Society of Hospital Pharmacists, clinicians, pharmacists, pharmacologists, informaticists, etc. the consensus process was enriched by consideration of a variety of perspectives. The result is a list that is easy to implement in any system without being limited by a specific medication knowledge base. Further work is needed to review the appropriate members within the classes expressed in the interaction pairs. The DDI set proposed here came from the database of one academic medical center and consisted of those DDI that are frequently overridden, which may limit generalizability. It remains to be studied whether there are differences between the override tolerances of providers who practice at academic medical centers and those who practice in the community. The panel represents diverse stakeholders whose perspectives could have ameliorated this limitation; however, empirical evaluation is needed to assess the utilization of the DDI list in actual clinical practice. Obtaining the alert override logs from actual clinical practice and assessing them in combination with literature evidence was very beneficial in assessing these interactions in addition to the characteristics of the interactions themselves. In order to assess the benefit of the list of alerts that can be safely made non-interruptive, further research is needed to evaluate providers' responses to this list and the consequent improvement in patient safety.

Creation of a list, such as the one described here, is a crucial but small step. Several processes need to be in place for the continued maintenance of this list over time. Making sure new interactions are added as drugs enter the market, assessing the membership within a drug class or modifying the severity grading assigned to an interaction as new evidence gets published, represent some of these processes. One recommendation is the formation of a private-public consortium, with diverse representation, such as the one described here, to enable the process of editing and maintaining this list. However, appropriate incentives need to be aligned to promote both participation in the process and the implementation of the list in EHR.

Furthermore, alert fatigue is a complex phenomenon, which occurs as a consequence of not just a high volume of alerts but also because of a human component associated with it. This human component drives the user to make the decision actually to read the alert and determine the helpfulness of the alert at the point of decision making. Implementation of a list, such as the one described here, would reduce the number of alerts seen by a provider and thus improve alert fatigue. The consequent impact of reducing the volume of alerts on the human element remains to be studied. Non-interruptive alerting can take various forms and further research is needed to understand the best way to surface the information on the DDI identified here, in the EHR. Such research should aim at determining the appropriate visual display for providing this information—whether it should be 'pushed' to the provider in a non-interruptive manner or whether the provider should be expected to look for it, if interested.

This study has several key limitations. The DDI came from only one large institution, and it is unclear what fraction of all DDI they would represent in other institutions. We utilized an expert panel process rather than a formal evidence review for the individual interactions because of resource limitations, which turned out to be successful as there was a high degree of consensus on the interactions presented.

CONCLUSION

This study highlights a process that can be employed for collaboration across entities to assess DDI alerts that can safely be made into non-interruptive alerts for CDS in EHR. We provide a list of interactions that can be safely suppressed from interruptive alerting and reduce alert fatigue.

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REFERENCES

- 1 Jha AK, Lagumette J, Seger A, *et al*. Can surveillance systems identify and avert adverse drug events? A prospective evaluation of a commercial application. *J Am Med Inform Assoc* 2008;15:647–53.
- 2 Hug BL, Witkowski DJ, Sox CM, *et al*. Adverse drug event rates in six community hospitals and the potential impact of computerized physician order entry for prevention. *J Gen Intern Med* 2010;25:31–8.

- 3 Lee EKM, Mejia AF, Senior T, *et al.* Improving patient safety through medical alert management: an automated decision tool to reduce alert fatigue. *AMIA Annu Symp Proc*; 2010:417–21.
- 4 Schedlbauer A, Prasad V, Mulvaney C, *et al.* What evidence supports the use of computerized alerts and prompts to improve clinicians' prescribing behavior? *J Am Med Inform Assoc* 2009;16:531–8.
- 5 van der Sijs H, Aarts J, Vulto A, *et al.* Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc* 2006;13:138–47.
- 6 Taylor LK, Tamblyn R. Reasons for physician non-adherence to electronic drug alerts. *Stud Health Technol Inform* 2004;107:1101–5.
- 7 Isaac T, Weissman JS, Davis RB, *et al.* Overrides of medication alerts in ambulatory care. *Arch Intern Med* 2009;169:305–11.
- 8 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;14:29–40.
- 9 RAND. Advancing clinical decision support. Contract # HHSP23320095649WC—Task order HHSP23337009T. (cited 21 Mar 2012). <http://www.rand.org/health/projects/clinical-decision-support.html>(accessed 18 September 2012)
- 10 Peterson JF, Bates DW. Preventable medication errors: identifying and eliminating serious drug interactions. *J Am Pharm Assoc (Wash)* 2001;41:159–60.
- 11 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;19:735–43.
- 12 van der Sijs H, Aarts J, van Gelder T, *et al.* Turning off frequently overridden drug alerts: limited opportunities for doing it safely. *J Am Med Inform Assoc* 2008;15:439–48.
- 13 Kesselheim AS, Cresswell K, Phansalkar S, *et al.* Clinical decision support systems could be modified to reduce 'alert fatigue' while still minimizing the risk of litigation. *Health Aff (Millwood)* 2011;30:2310–17.
- 14 Hazlet TK, Lee TA, Hansten PD, *et al.* Performance of community pharmacy drug interaction software. *J Am Pharm Assoc (Wash)* 2001;41:200–4.
- 15 Langdorf MI, Fox JC, Marwah RS, *et al.* Physician versus computer knowledge of potential drug interactions in the emergency department. *Acad Emerg Med* 2000;7:1321–9.
- 16 Del Fiol G, Rocha BH, Kuperman GJ, *et al.* Comparison of two knowledge bases on the detection of drug–drug interactions. *Proc AMIA Symp*; 2000:171–5.
- 17 Smith WD, Hatton RC, Fann AL, *et al.* Evaluation of drug interaction software to identify alerts for transplant medications. *Ann Pharmacother* 2005;39:45–50.
- 18 Fernando B, Savelyich BS, Avery AJ, *et al.* Prescribing safety features of general practice computer systems: evaluation using simulated test cases. *BMJ* 2004;328:1171–2.
- 19 van Roon EN, Flikweert S, le Comte M, *et al.* Clinical relevance of drug–drug interactions: a structured assessment procedure. *Drug Saf* 2005;28:1131–9.
- 20 Hansten PD, Horn JR, Hazlet TK. ORCA: OpeRational ClassificAtion of drug interactions. *J Am Pharm Assoc (Wash)* 2001;41:161–5.
- 21 Weingart SN, Simchowitz B, Shiman L, *et al.* Clinicians' assessments of electronic medication safety alerts in ambulatory care. *Arch Intern Med* 2009;169:1627–32.
- 22 van der Sijs H, Lammers L, van den Tweel A, *et al.* Time-dependent drug–drug interaction alerts in care provider order entry: software may inhibit medication error reductions. *J Am Med Inform Assoc* 2009;16:864–8.
- 23 **Institute for Safe Medication Practices.** *ISMP's List of High-Alert Medications.* 2012 (cited 22 March 2012). <http://www.ismp.org/Tools/highAlertMedications.asp> (accessed 18 September 2012)
- 24 Duke JD, Bolchini D. A successful model and visual design for creating context-aware drug–drug interaction alerts. *AMIA Annu Symp Proc*; 2011;339–48.
- 25 Scheepers-Hoeks AM, Grouls RJ, Neef C, *et al.* Strategy for implementation and first results of advanced clinical decision support in hospital pharmacy practice. *Stud Health Technol Inform* 2009;148:142–8.