

The Effect of Patient-Specific Drug-Drug Interaction Alerting on the Frequency of Alerts: A Pilot Study

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Abstract

Background: False-positive drug-drug interaction alerts are frequent and result in alert fatigue that can result in prescribers bypassing important alerts. Development of a method to present patient-appropriate alerts is needed to help restore alert relevance. **Objective:** The purpose of this study was to assess the potential for patient-specific drug-drug interaction (DDI) alerts to reduce alert burden. **Methods:** This project was conducted at a tertiary care medical center. Seven of the most frequently encountered DDI alerts were chosen for developing patient-specific, algorithm-based DDI alerts. For each of the DDI pairs, 2 algorithms featuring different values for modifying factors were made. DDI alerts from the 7 drug pairs were collected over 30 days. Outcome measures included the number of DDI alerts generated before and after patient-specific algorithm application to the same patients over the same time period. **Results:** A total of 14 algorithms were generated, and each was evaluated by comparing the number of alerts generated by our existing, customized clinical decision support (CDS) software and the patient-specific algorithms. The CDS DDI alerting software generated an average of 185.3 alerts per drug pair over the 30-day study period. Patient-specific algorithms reduced the number of alerts resulting from the algorithms by 11.3% to 93.5%. **Conclusion and Relevance:** Patient-specific DDI alerting is an innovative and effective approach to reduce the number of DDI alerts, may potentially increase the appropriateness of alerts, and may decrease the potential for alert fatigue.

Keywords

drug interactions, clinical decision support, alert fatigue, patient specific alerting, database customization

Introduction

Electronic medical records (EMRs) may benefit patient care in several ways, including providing alerts for potential drug-drug interactions (DDIs). These alerts are intended to inform health care providers of potential safety issues associated with drug combinations. Despite these alerts, DDIs have been shown to contribute to patient morbidity and mortality, length of stay, and cost of treatment. Several studies have reported adverse drug events associated hospital admissions that were attributable to DDIs.¹⁻⁵ With increasing numbers of available drugs and more potentially interacting drug pairings, patients are increasingly likely to be exposed to interacting drug pairs. Common potentially interacting drug pairs include angiotensin-converting enzyme inhibitors/diuretics, digoxin/loop diuretics, aspirin/heparin, and fluconazole/cyclosporine.⁶ Several of the potential interaction pairs noted in the studies cited above are frequently prescribed for therapeutic benefit or are dose dependent.

Alert fatigue, where the health care provider pays less attention to or ignores computer-generated alerts, occurs when alerts are considered excessive or irrelevant by the

provider. With alert fatigue, potentially dangerous interactions can be lost among the vast quantity of false-positive alerts that are not appropriate for the specific patient. Studies of health care provider responses to alerts have shown that 35% to 96% of DDI alerts are overridden.⁷⁻⁹ As a demonstration of alert fatigue, a study of alerts over a 36-week period showed a gradual decrease in responsiveness to the alerts.¹⁰ More important for patient care than the number of alert overrides is the appropriateness of the overrides. Inappropriate overrides have been reported to increase the risk of potential and definite adverse patient outcomes by 6-fold.⁸

Approaches to reduce the number of inappropriate alerts and increase the specificity of alerts shown to EMR users have been examined in several studies.¹¹⁻¹⁴ A study surveyed

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a panel of 18 physicians and 6 pharmacists to find commonly encountered DDI alerts that could be disabled completely. No consensus could be reached among the group to determine which alerts could be safely turned off.¹¹ Other approaches have included turning off alerts except for those with the highest severity rating in the software, turning off some alerts for physicians but not for pharmacists, and changing the severity ratings of selected alerts.¹⁵ These approaches all have potential limitations. Blocking all alerts except those with the highest severity rating may prevent alerting for risky drug combinations, such as colchicine/clarithromycin, aminophylline/ciprofloxacin, quinidine/clarithromycin, and valproic acid/carbapenems. This approach will put some patients at risk and should be avoided. Another approach to reduce excessive alerts is to restrict alerts that are displayed to prescribers but to present all alerts to pharmacists. This creates a burden on pharmacy to identify and evaluate risky interactions and then obtain prescriber agreement for management. Although end-user modification of severity class is an option for some CDS software, these are often limited in scope and methodology.

Some attempts to solve the alert fatigue problem have used more nuanced approaches to increasing the specificity and decreasing the volume of alerts. One such attempt used a panel of practitioners similar to the one mentioned above. Rather than trying to make a list of high-severity DDI alerts to turn off, the panel was able to come to a consensus about alerts that could be made noninterruptive.¹² In a retrospective study of 2 academic medical centers, one with tiered alerts and the other without, it was reported that splitting alerts into different tiers could reduce overrides for higher-risk drug interactions and improve medication selection.¹³ Tiering alerts based on the potential risk to patients has been done for many years in DDI references and is now standard in commercial CDS systems, but evidence of excessive alerts persist. More recently, a decision tool was created to identify the alerts that were most commonly overridden by users. The DDIs that users almost always override would then be filtered out to reduce alert fatigue.¹⁴

Methods

Prior Efforts to Customize DDI CDS

The site of this study is a medical center with 863 beds and approximately 34 000 yearly admissions. The medical center utilizes an EMR system that offers several clinical decision support (CDS) modules, including DDI checking. The medical center has established that DDI CDS requires an override reason for any potential DDI that has a severity classification of major. A potential DDI classified as major is one that requires some intervention to mitigate patient risk. Both prescribers and pharmacists see the same DDI alerts classified as major. The DDI database in use at the

medical center has been customized to limit the number of potential DDIs rated as major. This process has been described in detail elsewhere, but briefly, it involves an ongoing review of DDIs rated as major by the EMR vendor and reassessing the risk of the DDI to cause patient harm.¹⁶ The Operational Classification (ORCA) system is used to identify potential DDI pairs that should be avoided or require action to mitigate risk to patients (major) or can be prescribed with usual patient monitoring (moderate).¹⁷ As a result of the ongoing DDI CDS customization, approximately 62% of the individual drug pairs classified as major by the EMR vendor have been reclassified as moderate, markedly reducing the number of actionable DDI alerts presented to prescribers and pharmacists. This rather simplistic approach to reducing inappropriate alerting requires considerable effort to evaluate potential DDIs for severity class modification using primary literature sources where possible and to review monthly vendor supplied updates for customization.

A limitation to this approach is that alerts remain either “on” or “off” for all patients. Additional customization based on patient-specific factors and using systematic, evidence-based evaluation of DDI evidence has the potential to further reduce the number of inappropriate alerts.^{15,18,19} Several drug and patient factors can affect the magnitude of a potential DDI and, therefore, the potential risk to the patient of an adverse outcome. Drug factors include the dose of the object and precipitant drug, route of administration, drug formulation, order of drug administration, and duration of drug administration. Patient factors consist of phenotype of elimination pathways, gender, vital signs, and comorbid conditions.²⁰

Patient-Specific DDI Alerting

The purpose of this pilot project was to assess the potential for patient-specific DDI alerts to reduce the total alert burden by alerting only for those patients at greatest risk for an adverse outcome. This project was determined to be exempt by the medical center institutional review board.

All DDI alerts classified as major for inpatients were collected for 30 consecutive days. Based on the frequency of alerts generated for inpatients, we identified 7 DDI pairs to test with patient-specific algorithms. The pairs (precipitant drug/object drug) include ciprofloxacin/oxycodone, fluconazole/oxycodone, diltiazem/oxycodone, fluconazole/fentanyl, amiodarone/oxycodone, fluconazole/tacrolimus, and amlodipine/simvastatin. These pairs differ from those usually identified as commonly occurring alerts because of the previously described database customization that eliminated many common but often inappropriate alerts.

The pharmacological and interactive properties of the 7 drug pairs were reviewed. Potential drug and patient-modifying factors were evaluated to identify those that appeared to

have the greatest effect on the risk of the DDI to cause patient harm. For the DDI pairs identified above, dose, bed location, and drug formulation were the modifying factors most often identified. For the purpose of this study, some of the modifying factors were assigned varying values to demonstrate the effects of using different values of the same variable in the algorithm. For example, the dose of the object or precipitant drug selected for the algorithm could vary. Therefore, all study DDI pairs were evaluated twice, each time with a different value for the modifying factor drug dose.

As an example of DDI-modifying factors, fluconazole-mediated inhibition of CYP3A4 is dose dependent. At doses less than 200 mg/d, fluconazole has demonstrated limited effect on CYP3A4 substrates. A fluconazole dose of 100 mg/d had minimal effect on cyclosporine elimination.^{21,22} CYP3A4 substrates with high first-pass elimination will be more sensitive to concurrent fluconazole administration when they are administered orally. A single oral 150-mg dose of fluconazole increased the mean area under the curve (AUC) of the orally administered, sensitive CYP3A4 substrate midazolam by less than 50%.²³ A daily 100-mg dose of fluconazole increased the mean AUC of triazolam approximately 2-fold, whereas a 200-mg/d dose resulted in a 4.4-fold increase.²⁴ Based on the interacting properties of fluconazole, selecting different values for the fluconazole dose (eg, <200 mg/d or \leq 200 mg/d) in the algorithm that generates a DDI alert may be appropriate. In addition, the properties of the object drug should be considered when setting dose values that generate an alert. Low doses of oxycodone are less likely to produce an adverse outcome with fluconazole than high doses. Oxycodone is metabolized by both CYP3A4 and CYP2D6. Thus, a drug that inhibits both oxycodone metabolic pathways might be riskier to a patient than one that inhibits only a single pathway. The algorithm dose limit for oxycodone could be lower when the precipitant drug is a dual-pathway inhibitor and higher for a single-pathway inhibitor. Figure 1 is an example of the algorithm for low-dose fluconazole and low-dose oxycodone.

For each DDI pair, an algorithm was created by the authors to represent the modifying factors that could alter the risk to a patient of the interaction. When available, primary literature or studies done as part of the new drug application describing the interaction were used to identify and quantitate modifying variables. Clinical judgment was included when appropriate. For example, DDIs involving opioids for patients in intensive care units (ICUs) compared with a general hospital ward were not considered to be as risky because the ICU patients have more frequent and thorough monitoring for signs of excess opioid response.

The effect of patient-specific DDI alerting was assessed by comparing the number of DDI alerts generated for each target drug pair by the standard DDI CDS and the simulated application of the patient-specific algorithms over the same 30-day study period in the same patients. Descriptive

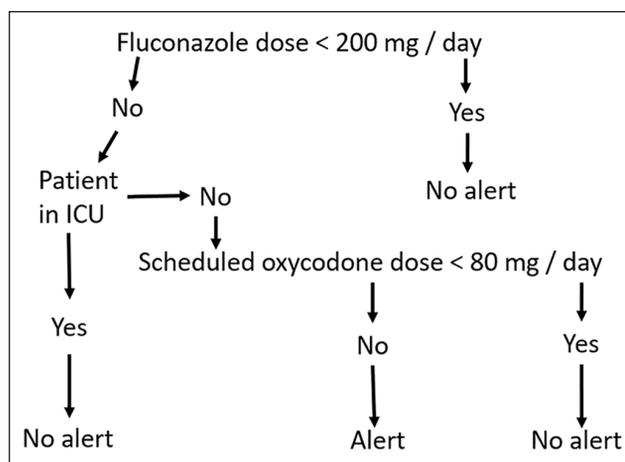


Figure 1. Algorithm for low-dose fluconazole/oxycodone interaction.

Abbreviation: ICU, intensive care unit.

statistics are used to describe the effects of the patient-specific DDI alerts on alert frequency.

Results

For each of the 7 drug pairs (which represent 21.7% of 5967 total major DDI alerts generated over the 30 days), algorithms were assessed using variable drug dose values to generate an alert. The dose values are either high dose (eg, fluconazole \geq 200 mg/d) or low dose (eg, fluconazole < 200 mg/d). A total of 14 patient-specific DDI alerts were evaluated.

Table 1 summarizes the effects of DDI filtering on the number of alerts presented to prescribers. Prior to filtering, the number of alerts generated by each of the 7 drug pairs averaged 185.3 (range 78-367) per drug pair during the standard DDI CDS alerting period. When the patient-specific algorithms were applied, the reduction in the individual alerts ranged from 11.3% to 93.5%. The mean number of alerts with high-dose algorithms was reduced by 60.2%, resulting in a mean of 73.7 alerts generated. The mean number of alerts with low-dose algorithms was 121.3, an average reduction in alerts of 34.5%. The mean difference in the percentage reduction in alerts between the high- and low-dose algorithms was 22.2% (range 8.3%-35.7%). The fluconazole/oxycodone algorithm reduced the number of alerts from the standard DDI CDS by 11.3% when the fluconazole dose was set at <200 mg/d, but 43.9% fewer alerts were generated when the fluconazole dose was set at \leq 200 mg/d compared with the standard CDS.

Discussion

Based on the results of this project, patient-specific DDI alerting can provide improved appropriateness of DDI alerts and a decreased volume of alerts. Our analysis showed

Table 1. Effect of Patient-Specific Alerting on Number of Alerts.

| DDI Drug Pairs and Dose | Standard CDS Alerts Generated, n | Patient-Specific Alerts Eliminated, n (%) |
|---|----------------------------------|---|
| Amlodipine/Simvastatin \leq 40 mg | 78 | 73 (93.5) |
| Amiodarone/Oxycodone \leq 40 mg | 146 | 64 (43.8) |
| Ciprofloxacin/Oxycodone \leq 80 mg | 130 | 100 (76.9) |
| Diltiazem/Oxycodone \leq 80 mg | 171 | 135 (78.9) |
| Fluconazole \leq 200 mg/Fentanyl | 367 | 179 (48.8) |
| Fluconazole \leq 200 mg/Oxycodone $<$ 80 mg | 246 | 108 (43.9) |
| Fluconazole \leq 200 mg/Tacrolimus | 159 | 122 (76.7) |
| Total | 1297 | 781 (60.2) |
| Amlodipine/Simvastatin $<$40 mg^a | 78 | 60 (76.9) |
| Amiodarone/Oxycodone $<$40 mg^a | 146 | 49 (33.5) |
| Ciprofloxacin/Oxycodone $<$80 mg^a | 130 | 68 (52.3) |
| Diltiazem/Oxycodone $<$80 mg^a | 171 | 111 (64.9) |
| Fluconazole $<$200 mg/Fentanyl^a | 367 | 48 (13.1) |
| Fluconazole $<$200 mg/Oxycodone $<$80 mg^a | 246 | 28 (11.3) |
| Fluconazole $<$200 mg/Tacrolimus^a | 159 | 84 (52.8) |
| Total | 1297 | 448 (34.5) |

Abbreviations: CDS, clinical decision support; DDI, drug-drug interaction.

^aLow drug dose used in algorithm.

a reduction of up to 93.5% of the study drug pair alerts generated by patient-specific algorithms compared with the standard DDI CDS. This reduction in alert volume is in addition to the reduced alerting subsequent to ongoing inhouse database customization. A prior study estimated that about 80% of common DDI alerts could be reduced in severity using modifying factors such as dosage, laboratory values, and concurrent medications.²⁵ Although these modifying factors were not applied to actual patients, the estimated results are generally in agreement with our findings. Kahan et al²⁶ studied the effect of a drug interaction CDS that used patient-specific parameters to generate DDI alerts in an ambulatory health maintenance system.²⁶ They reported a 42% reduction in alerts and significant reductions in hospitalizations and medication use in patients whose physicians were exposed to the software using patient-specific alerting.

We chose to study the effect of different values for the variables used in the alert algorithms because identifying precise values that define risk is difficult. Although it is obvious that some variables will have a major role in determining risk (eg, dose of the precipitant drug), dose-response data necessary to clearly define the critical dose are unavailable as a result of lack of data or confounders such as genetic polymorphisms in elimination pathways. It is important to note that the algorithm variables can be changed to reflect new data or improved understanding of the risks associated with a potential DDI. An additional benefit of patient-specific alerting is the ability to provide more explicit management options and guidance to the practitioner.

There were several limitations associated with this project. We were unable to assess the clinical significance of the DDI alerts or the effect of the patient-specific alerting on patient outcomes. This would be an important assessment but was beyond the scope of this pilot project. Because we had previously customized our DDI database by reducing the severity classification of almost two-thirds of the drug pairs originally classified as major, it is unknown what effect this approach would have on alert volume in a typical DDI database. Although the effect on the DDI pairs studied in this project would likely be similar, we would expect that many other potential DDIs could be identified for algorithm-based alerting. None of the algorithms we developed for the test DDI pairs used laboratory values as modifying parameters for alert generation. However, such algorithms are not difficult to develop but do require access to current patient data outside of drug administration records. Our EMR does not currently enable access to patient-specific laboratory values.

Software enabling automated access to a patient's EMR would provide the data needed to expand the number of potential DDI pairs that could be subjected to patient-specific alerting. Assessment of the dosage, route of administration and timing of the potentially interacting drugs, and laboratory values would be important factors in assessing potential risk. When a decision is made to override an alert, automated assessment of outcome measures, such as international normalized ratio for warfarin interactions or potassium concentrations when hyperkalemia is a risk, would identify patients experiencing an adverse response and those with minimal response to the potential DDI. These

approaches to DDI alerting would be a major advance in the provision of CDS for drug-related problems and should be standard in CDS software.

Conclusion and Relevance

Our pilot study has demonstrated the efficacy of patient-specific alerting to reduce the number of DDI alerts generated in an inpatient setting. The decrease in alert volume resulting from patient-specific alerting makes this new approach an exciting opportunity to both reduce alert fatigue and present alerts that are more specific to individual patients. The implementation of algorithm-generated patient-specific DDI alerts should be considered as a primary method to reduce alert fatigue and improve patient care.

Authors' Note

At the time this study was conducted, Stephen Ueng was a PGY-1 resident at UW Medicine Pharmacy Services.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: John Horn is a partner in H&H Publications, LLP, which publishes drug interaction references and provides consulting services related to drug interactions. Dr Horn has served as a consultant to Mediseen eHealth Ltd.

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