**Critical National Need**

# Implementing Personalized Medication Safety

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Key Words: Drug Safety, Adverse Drug Events, Computerized Physician Order Entry

## Summary

Drug safety is an area of critical national need because at least 1.5 million preventable adverse drug events are estimated to occur yearly in the United States. These events add over $3.5 billion dollars a year to the cost of healthcare. Barriers to improving drug safety include flaws within current clinical decision support and computerized order entry systems that impede these systems from significantly impacting the incidence of preventable adverse drug events. This white paper highlights some known weaknesses of current systems and identifies the potential solutions that may finally allow the hope of improved medication safety to be realized. Transformative collaborative research involving expertise in drug safety and informatics from within both academic and industry is needed to develop effective tools to improve safe prescribing.


## Introduction

It is estimated that at least 1.5 million preventable adverse drug events occur yearly in patients hospitalized in the United States. The Institute of Medicine's recent report, *Preventing Medication Errors: Quality Chasm Series* estimated the cost of preventable adverse drug events occurring in U.S. hospitals at $3.5 billion per year.[1] This pivotal report identified computerized order entry (CPOE) with clinical decision support (CDS) systems as a key prevention strategy for reduction in adverse drug events. Government agencies and other stakeholders have pushed implementation of electronic medical records and CPOE in part due for their potential to reduce these errors. Certainly, implementation of CPOE with CDS has successfully addressed some types of preventable drug adverse events such as therapeutic duplication. However, the incidence of other types of adverse drug events including drug-drug interactions has not been significantly impacted by CPOE. In fact, the recent report from the Veterans Administration highlights that CPOE can introduce serious new medication errors.[2]

Significant barriers to the optimal implementation of CPOE systems have been identified. Many of the difficulties associated with CPOE center around the drug safety alerting systems utilized in CDS and the workflow limitations resulting from adaptation of legacy computerized ordering for physicians. Major weaknesses of CDS include incomplete, inaccurate information and lack of clinical relevancy. The final step to improve medication safety is to design CPOE systems that address work-flow limitations, limit potential systems errors and fully utilize the electronic medical record to provide personalized clinical decision support.

## Current Resources are Incomplete

Acquisition of pharmaceutical knowledge is one of the most challenging aspects of CDS.[3] There is no resource that compiles the totality of published safety information. Certainly, approved prescribing information is not a definitive resource for drug safety information including drug-drug interactions. In fact, one evaluation of prescribing information found that only 33% of selected clinically relevant drug interactions were provided in the labeling information.[4] Incomplete information comprises a significant

problem for other aspects of drug safety especially pregnancy and lactation safety. Currently there is no systematic process to add new data once a drug has been approved. New information rarely is added to existing prescribing information unless it attracts the attention of the Federal Drug Administration (FDA) due to publicized safety issues.

Commercial drug compendia do not perform better than FDA approved prescribing information. A review of four major drug references found they failed to include selected clinically significant drug interactions 42 – 91% of the time.[5] Although the sources for commercially available databases such as First DataBank or Epocrates are not transparent, it is clear from comparing them to the approved prescribing information that they are substantially based on the product labeling. Therefore it is not surprising that current drug compendia also perform poorly in completeness. Commercially available resources perform poorly especially in specialized populations. For example, a review of one of the most popular commercial databases found that it failed to identify 70% of clinically significant drug interactions in transplant patients.[6]

The most immediate means to improve drug safety decision support is to implement established informatics techniques to systematically mine and add relevant information to drug safety compendia. Initial research in rule-based computer support has demonstrated considerable potential in filling this gap in completeness.[7,8]

## Current Compendia Contain Inaccurate Information

Current compendia frequently contain information that is factually inaccurate. For example, they often contain class effect warnings that in actuality only apply to a few drugs in the therapeutic class. This is prevalent among pharmacokinetic and pharmacodynamic warnings. For example, the labeling for VFEND® (voriconazole) states, "Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of statins that are metabolized by CYP3A4. It is recommended that dose adjustment of the statin be considered during co-administration. Increased statin concentrations in plasma have been associated with rhabdomyolysis".[9] The problem with this prediction is that it assumes that all statins metabolized by the enzyme (P450 CYP3A4) will exhibit clinically significant increases in concentration in the presence of that voriconazole. In fact, this prediction may only apply to two drugs in this therapeutic class (lovastatin and simvastatin). Even allergy alerts which would seem to be a straight-forward process have been plagued with major shortcomings.[10] In a review of CDS allergy alerts, only 10% of alerts were triggered by an exact match between the drug ordered and the listed allergy.[11] Examination of prescribing information and most commercial alerting systems finds little risk differentiation between different drugs in the same therapeutic class or even among therapeutic classes even when data indicate marked differences. For example, most product labels and commercial alerting systems do not differentiate the risk associated with "sulfa allergy" between sulfonamide antibiotics and non-antibiotic sulfonamide derivatives such as protease inhibitors and diuretics such as furosemide and hydrochlorothiazide at the same level. However, there is published evidence that the risk associated with non-antibiotic sulfonamide derivatives

is markedly less.[12] Furthermore, most applications do not distinguish between drug allergies and drug sensitivities.[13] This may be a critical distinction when faced with limited therapeutic options such as the post-operative patient needing pain control who previously experienced nausea when administered codeine who is now deemed to have an allergy to narcotics.

This type of information deficit is largely due to lack of expertise in pharmacology. Principles of metabolic drug interactions, transport drug interactions, allergic reactions and toxicity can be predicted from in vitro and in vivo experiments. In many cases, these principles have already been sanctioned and supported by the FDA. Design features of current CDS systems do not incorporate or compile this type of information. In contrast, initial research in predicting metabolic drug interactions from rule-based computer support based on metabolic principles has demonstrated considerable potential.[7,8] The principles of rule-based support can be applied to other aspects of drug safety.

## Current Compendia Contain Clinically Irrelevant Alerts

Many safety alerts found in prescribing information and drug compendia are viewed by physicians and drug safety experts as not clinically relevant.[14] Nuisance alerts can potentially create several problems for a CDS/CPOE system including disenfranchisement with both the alert system and the CPOE system in general.[3] Physicians frequently override alerts they perceive as irrelevant, (up to 88-89% of all alerts).[15,16] The workflow disruption involved in overriding a non-relevant alert has been a major source of physician dissatisfaction with the current CDS systems.[9] This dissatisfaction has lead to inactivation of the clinical decision support systems in major hospital systems.

The hypothesis that engagement of experts in translational and clinical medicine is important is supported by performance data of drug safety compendia developed by institutions that have utilized this expertise. In comparison to commercial drug compendia, systems developed by academic or non-profit centers have more successfully addressed the issue of completeness and false-positive drug safety alerts.[17] They appear to have more credibility with physicians as evidenced by the lower override rates.[18] But at the same time these home-grown systems have not achieved generalizable compatibility with the commercial healthcare information systems available today. One measure that may produce a rapid improvement in drug safety alerting systems is to encourage collaborations between selected academic and commercial healthcare information developers.

## Current Decision Support is Not Fully Personalized

Although academic/industry collaborations offer the promise of more complete and accurate drug safety databases, the potential that collaborations between drug safety experts and information technology can offer to drug safety has yet to be realized. Personalized medicine is a term associated with the promise of optimized drug selection in the future. The data needed to implement personalized drug safety alerting already

exists. We know that specialized populations such as infants, elderly or patients with renal and liver dysfunction often fail to eliminate drugs from the body as well as adults with normal kidney and liver function. This means they may develop toxic drug levels at the dosages normally utilized in the general population. Furthermore, it is known that other populations such as patients with congestive heart failure are likely to experience severe adverse side effects at dosages that would be tolerated in healthy individuals. Implementation of personalized medications and dosages has the tremendous potential to markedly impact the incidence of serious adverse drug events.

CDS with rules engine logic to provide rudimentary customized alerts has been effective in reducing some types of medication errors. [19] The question becomes "Why has customization not been adopted universally?" Current drug safety compendia offer a relatively flat design. Although they may contain sporadic comments regarding drug safety in specialized populations, this information is sparse and requires the provider to hunt through the text to find it. But more importantly, there has been little emphasize on mining the electronic medical record to populate a rule-based customized decision support system.

Currently, personalized medication safety depends on the expertise of the pharmacist and physician. As a consequence, this introduces the possibility for systems error, i.e. if the human expert is distracted or in reality, inexperienced, this type of medication error may not be detected a priori. This suggests that major steps in drug safety improvement could be made if key data such as age, calculated renal clearance and major diagnoses are imported from the electronic medical record and utilized to drive the clinical decision support system.

The drug pair, digoxin-clarithromycin, vividly illustrates the interplay between patient risk factors and drug interactions. Digoxin is a medication utilized in some cardiac conditions and has a narrow therapeutic range where plasma levels only slightly above the levels needed for efficacy may produce severe and even fatal side effects. Clarithromycin is an antibiotic frequently utilized as part of the treatment protocol for Helicobacter pylori infection, a bacteria infection associated with peptic ulcer disease. There is concern that administering digoxin and clarithromycin at the same time may lead to high digoxin concentrations. The alert system, First Databank, ranks this drug pair interaction as severe and recommends that digoxin levels should be monitored. Similarly, the product label for clarithromycin also recommends, "Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously".[20] These alerts represent both over and under alerting depending on the route of digoxin administration and the patient's renal function. Clinical studies of this drug pair have demonstrated relatively modest increases in digoxin levels among subjects with normal renal function (35 – 64% increase in plasma concentration over time).[21,22,23] However, a recent case series evaluating this drug pair in patients with end-stage renal disease reported digoxin level increases of up to 4 fold, with levels continuing to rise up to three days after digoxin was discontinued.[24] The data suggest this interaction could be managed by a reduction in digoxin dosage and close monitoring of digoxin levels in patients with normal kidney function. On the other hand, in patients with renal

insufficiency the most appropriate recommendation is to avoid this combination completely due to the profound and prolonged effect on digoxin pharmacokinetics. It is not appropriate to recommend continued administration with monitoring in this patient population.

The challenge of personalizing drug prescribing is the tremendous IT support required to pull data from the electronic medical record. This type of IT investment is beyond the reach of most academic institutions and funding opportunities. Therefore, successful implementation will require a collaborative effort between academic institutions and commercial healthcare information systems and a new type of government funding.

## Putting It All Together

Incorporating complete, accurate, clinically relevant personalized drug safety information could markedly improve patient safety. But one final intervention that could impact both drug safety and best medical practice is to think in terms of best clinical support instead of just drug safety . Current drug compendia typically express warning in terms of absolutes. In other words, they state that certain drug pairs must not be co-administered. But this type of flat, non-adaptive warning ignores the reality of the practice of medicine. The provider often must weigh the optimum treatment of disease against potential medication risks. For optimal treatment of diseases such as AIDS, stroke, atrial fibrillation, severe infections or seizure disorders, some risk of drug interactions or adverse drug events must be accepted. Therefore, the most appropriate course of action might be dosage reduction, increased monitoring including drug levels or other tests. If best practices could be implemented at the time of drug ordering they have the potential to both improve work flow and decrease adverse drug events.

The previous drug interaction example of digoxin and clarithromycin can be utilized to illustrate how branched, personalized clinical decision support might work. There may be cases where a provider might choose to utilize clarithromycin to treat ulcer-associated Heliobacter pylori infections due to other patient factors even if the patient is taking digoxin. Since this drug pair can be managed safely in patients with normal renal function, the most appropriate action would be to return a warning to monitor digoxin levels closely. Alternatively, since there is clear evidence that this combination is unsafe in patients with renal dysfunction, the most appropriate action would be to prohibit addition of clarithromycin to the patient's regimen. In the typical CPOE system, the provider would receive the same alert if they added clarithromycin to the drug regimen of a patient taking digoxin regardless of the patient's renal function. It is up to the provider to remember to check the patient's renal function, reduce the dosage and order frequent digoxin levels to monitor the interaction. If instead the system automatically monitored renal function and existing digoxin dosage, it could either return a warning that the drug pair was prohibited in the case of a patient with renal failure or return a warning that a digoxin dosage reduction was recommended. In the latter, a preemptive warning could also be sent to the pharmacy department to check whether the dosage had been appropriately decreased. Finally the system could automate the ordering of more frequent digoxin levels instead of requiring the provider to switch their workflow from drug order

entry to laboratory test ordering. This would appear to be an inconsequential step but in reality may take more than a few minutes in some CPOE systems. Finally, an automated monitoring system could monitor when changes in drug levels or renal function hit pre-determined limits. For example, in the case of our drug pair, both the provider and pharmacy departments could be notified when there is a 20% change in plasma digoxin levels (since it is a narrow therapeutic range drug where small changes in drug levels can result in toxicity) or renal function so that changes in drug regimen could be made more proactively. The following figures illustrate a current alert and how a granular hypothetical alert system might work.

Figure1. Current Drug Alert for Digoxin-Clarithromycin

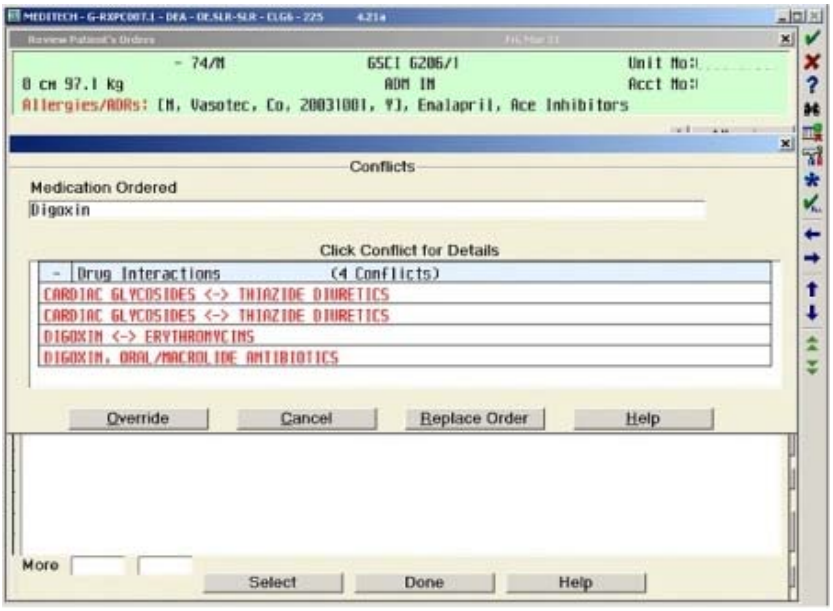
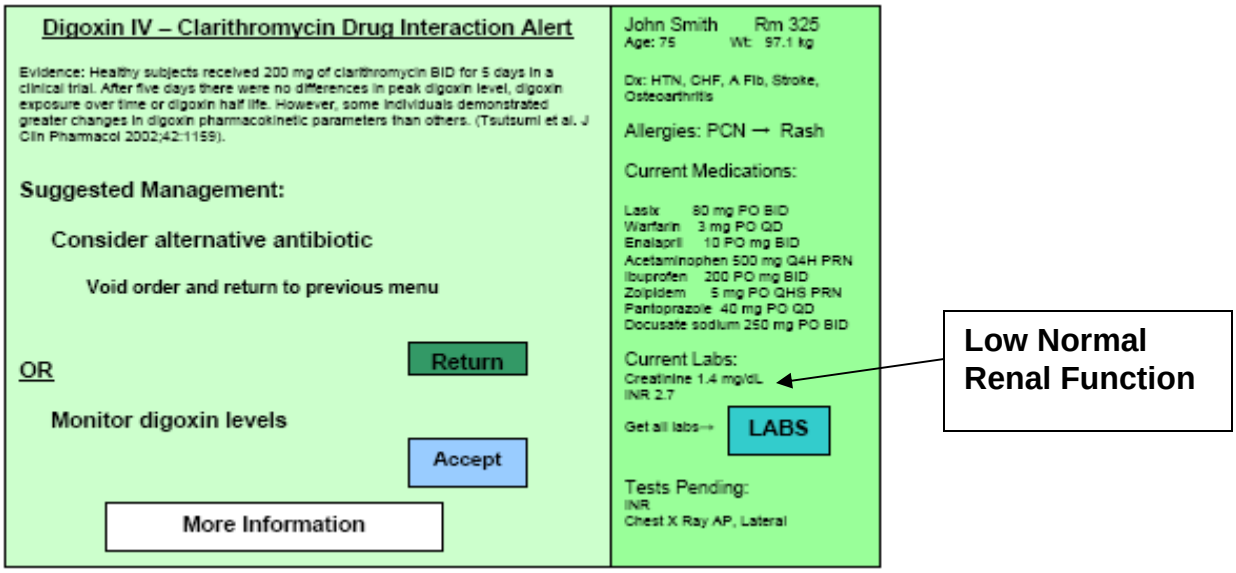


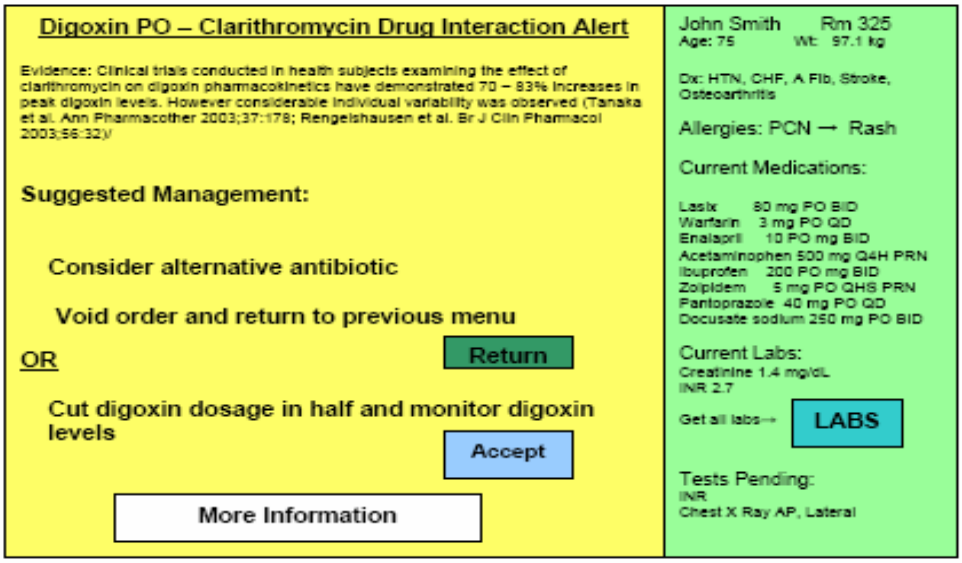

Figure 1 illustrates the alert for the drug pair, digoxin and clarithromycin for a major commercial CDS/CPOE system. Although it does show current medications and does allow for the provider to obtain more information regarding the alert, it provides the same warning for all patients and all routes of administration. If the provider wishes to check the patient's renal function in order to determine the degree of risk they must either go to the paper chart or other portions of the electronic medical record to estimate this parameter. If the provider then decides that this combination may be safety managed with increased laboratory monitoring of digoxin levels they must then go to yet another part of the CPOE system to order these tests.

Figure 2. Hypothetical Digoxin/Clarithromycin Alert, Intravenous administration digoxin



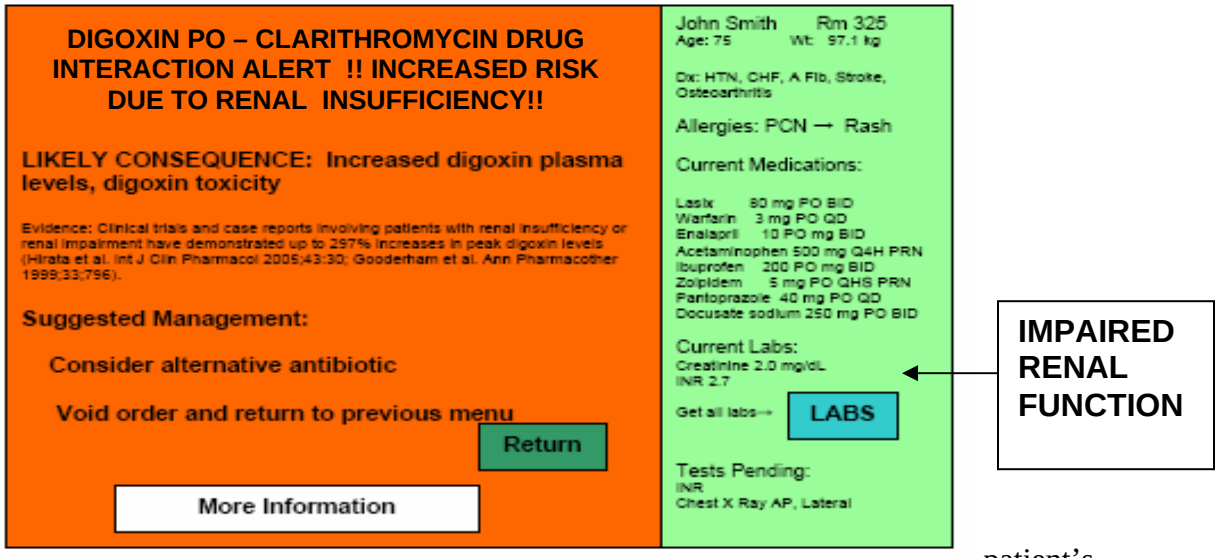

In Figure 2 the hypothetical alert for intravenous administration of digoxin with clarithromycin, key demographics of the patient such as current laboratory values, pending tests, age and weight are available to the provider throughout CPOE. The system has also estimated the patient's renal function using the Cockcroft-Gault Equation and categorized the patient as having low normal kidney function. Data indicate that the increase in digoxin levels is highly variable depending on whether the digoxin is administered orally or intravenously with much smaller increases during intravenous digoxin administration. Therefore this alert for intravenous administration of digoxin is categorized by the decision support system as potentially clinical significant but manageable. The provider is given the options of ordering an alternative antibiotic or monitoring digoxin levels on a schedule previously determined to be best practice by the pharmacy committee of the hospital.

Figure 3. Hypothetical Digoxin/Clarithromycin Alert, Orally administered digoxin



In Figure 3 the route of digoxin administration has switched from intravenous to oral which increases the potential for digoxin toxicity. The background color of the screen has changed from green to yellow in order to make it readily recognizable that the level of the drug alert has increased. In this case, the provider has the option to void the order and prescribe another antibiotic. Alternatively, they may continue with the clarithromycin order by halving the digoxin dosage and instituting a monitoring schedule of digoxin levels.

Figure 4 Hypothetical Digoxin/Clarithromycin Alert, Oral administration, Renal Insufficiency




In the final example, the route of digoxin administration is also oral but the patient's kidney function as measured by creatinine clearance has decreased to 64.69 mL/min. Since the risk of digoxin toxicity is now likely even with dosage reduction, best practice would not allow this combination to be prescribed. The background of the webpage is now shaded orange to make the severity of the alert readily apparent.

## Conclusion

Preventable adverse drug events represent an area of critical national need due to the tremendous number of people affected by these events and the vast expense involved. The societal challenge in reducing these events is confronting the flaws in current CDS/CPOE systems. The logic of drug safety support is complex. Recommendations must utilize patient-specific reasoning. Finally there must be better integration with the entire CPOE system so that alerts facilitate appropriate related actions, not just check drug orders. Transformative results are possible if collaborative research involving expertise in drug safety and informatics from within both academic and industry is funded.

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