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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

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Abstract

Background: Computerized physician order entry systems are known to improve patient safety in acute-care hospitals. However, as clinicians frequently override drug interaction and allergy alerts, their value in ambulatory care remains uncertain.

Objective: The purpose of the study was to examine whether ambulatory care clinicians were more likely to accept drug-drug interaction alerts that an expert panel judged to be of high clinical value.

Study Design: We convened an expert panel to examine drug-drug interaction alerts generated by 2872 clinicians in Massachusetts, Pennsylvania and New Jersey who used a common electronic prescribing system between 1 January 2006 and 30 September 2006. We selected 120 representative drug interaction alerts from the most commonly encountered class-class interactions.

Measurements: The expert panel rated each alert based on the following categories: (i) strength of the scientific evidence; (ii) probability that the interaction would result in an adverse drug event (ADE); (iii) severity of typical and most serious ADEs; (iv) the likelihood that a clinician could act on the information; and (v) the overall value of the alert to the average primary care clinician. We then used multivariate regression techniques to examine the relationship between the alert acceptance rate and the expert panel's mean rating of each category.

Results: The decision of clinicians to accept drug interaction alerts increased (relative to a baseline alert acceptance rate of 8.8%) by 2.7% (95% CI 0.4, 5.1) for interactions that panelists judged would result in an ADE, by 2.3% (95% CI 0.9, 3.7) when primary care providers (PCPs) lacked prior knowledge about the information presented in the alert, and by 3.3% (95% CI 0.9, 5.8) when the PCP could readily act on the information provided in the alert.

Conclusion: The value of electronic drug interaction alerts is influenced heavily by clinicians' judgements about the clinical value of the alert. Expert judgement should be taken into account when developing electronic decision support.

Background

Although computerized physician order entry systems have been shown to improve patient safety in acute-care hospitals, their value in ambulatory care remains uncertain.[1,2] Clinicians override drug interaction and allergy alerts at rates as high as 90%,[3-5] suggesting that the clinical utility of these alerts may be limited. Indeed, in a variety of surveys and focus group studies,[6-10] clinicians regularly report that drug interaction alerts and advanced decision support features are disruptive, do not provide appropriate information and fail to take into account the patient's clinical context or medical history. If the majority of medication safety alerts lack value to clinicians, they may contribute little to patient safety and compromise the impact of critical alerts.

We hypothesized that clinicians' decisions to accept drug-drug interaction alerts would be strongly influenced by their perceived clinical value. High-value alerts, defined as alerts that are based on sound empirical evidence, that identify potentially serious and preventable adverse events and that have a significant probability of harm, would be accepted at higher rates than alerts without these features. To test this hypothesis, we assembled an expert panel to judge the value of a group of frequently encountered electronic drug interaction alerts, and then examined the relationship between the expert panel's judgements and ambulatory care clinicians' decisions to accept these drug interaction alerts.

Methods

E-Prescribing System

We obtained information on 229 663 electronic drug-drug interaction alerts generated from 1 January 2006 to 30 September 2006 by 2872 ambulatory clinicians in Massachusetts, Pennsylvania and New Jersey who used a common electronic prescribing system called PocketScript (ZixCorp, Dallas, TX, USA).[5] The system includes a variety of standard features, including medication pick lists with default dosing, the ability to create favourite prescriptions, formulary tiers tied to patient's insurance type and the ability to transmit prescriptions to the pharmacy electronically.

The system provides drug interaction and allergy alerts when a clinician attempts to write a prescription. The system checks whether the new medication interacts with any medication on the patient's active drug list, based on a list of medication interactions maintained by Cerner Multum (Denver, CO, USA). If an interaction is identified, the system displays a warning with the severity of the interaction (high, medium or low) and the clinician can choose to view a written description of the interaction. The clinician has three options after encountering an alert. He or she may (i) override the alert and continue with the prescription; (ii) change the prescription to another drug; or (iii) cancel the prescription. We combined (ii) and (iii) and denote these events as 'accepted' alerts.

Selection of Alerts

Of the drug-drug interactions encountered by the 2872 clinicians, approximately 62% were high severity, 30% were moderate severity and 8% were low severity.[5] We had our expert panel review a sample of 80 high severity, 20 medium severity and 20 low severity drug-drug interaction alerts. We focused more heavily on high severity alerts given their clinical importance and the high proportion of these alerts encountered in clinical care. For each alert severity level, we sorted alerts by the interacting classes of medications and then ordered the classes by how often they were encountered. We then selected the most commonly encountered drug-drug interaction pair within each class-class interaction.

Expert Panel Review

We recruited an expert panel of five clinicians with experience in primary care, pharmacy, medication safety and health administration. The reviewers discussed the project individually with the principal investigator and participated in a 1-hour conference call to review the project, task, instrument and rating categories, and to practice sample cases.

Panelists were instructed to evaluate each interaction on the basis of their own professional experience. We provided each reviewer with the alerted drug-drug interaction, the class-class interaction from which it was drawn and the text of the drug interaction alert. Panelists also received a document, arranged by drug interaction, with excerpts from four pharmaceutical references: Micromedex (Thomson Reuters Healthcare, New York, NY, USA), Clinical Pharmacology (Gold Standard, Tampa, FL, USA), Lexi-Comp (Lexi-Comp, Inc., Hudson, OH, USA) and Epocrates (Epocrates, Inc., San Mateo, CA, USA). The excerpts included verbatim descriptions of each interaction from the references, with information about the type of interaction and its pharmacological or epidemiological basis. Panelists were permitted, but not required, to review reference material, including the resources we provided.

Panelists made judgements about several alert attributes. First, they rated the strength of the scientific evidence for the interaction on a 3-point scale (weak, moderate, strong). Weak evidence was supported by no data, 'mechanistic' evidence such as the cytochrome P450 metabolism or other pharmacological properties of the drugs. Case reports of adverse events in humans denoted moderate evidence. Strong evidence was supported by published epidemiological studies or clinical trials, or an interaction that is seen commonly in clinical practice.

Second, we asked panelists to estimate the probability that the interaction would result in an adverse drug event (ADE) requiring medical attention (rare, intermediate, common). Panelists rated the interaction as 'rare' if it was estimated to occur in less than 1% of patients. Intermediate probability occurred between 1 and 10% of patients, and common events occurred in more than 10% of patients.

Third, panelists indicated whether the information was well known to an average primary care provider (PCP) on a 4-point scale (definitely, probably, probably not, definitely not).

Fourth, panelists judged the severity of ADEs that resulted from the interaction based on a 5-point scale derived from previous studies of ADEs in ambulatory care (life threatening, serious, significant, minor or trivial, no harm).[11] They judged the severity of the typical ADE that resulted from the interaction and then the most serious possible event. Life-threatening events included stroke, myocardial infarction or anaphylaxis. Serious events affected organ system function and included, for example, delirium, renal failure or deep vein thrombosis. Significant events produced symptoms such as fever, myalgias or pruritis. Minor or trivial events caused minimal discomfort such as swallowing a tablet. Reviewers could also judge that the typical or most severe possible event produced no harmful consequences.

Fifth, panelists judged whether a clinician could act on the information provided in the alert (definitely, probably, probably not, definitely not) by prescribing an alternate medication, choosing a non-pharmacological therapy, ordering laboratory tests or monitoring the patient more closely. Finally, panelists judged the overall value of the alert to the average primary care clinician (definitely, probably, probably not, definitely not). Panelists completed their ratings independently, and were blinded to the Cerner Multum alert severity designation.

Data Analyses

We collected panelists' ratings and entered them into an electronic spreadsheet. To calculate interrater reliability, we dichotomized 4-item responses (definitely, probably, probably not, definitely not) into two categories (definitely/probably, probably not/definitely not). We collapsed 5-item responses (life threatening, serious, significant, minor/trivial, not harmful) into three categories (life threatening or serious, significant, minor/trivial or no harm). We calculated interrater reliability for each rating category (scientific evidence, likelihood, familiarity to clinician, severity, ability to act on the in-

formation and overall value) using the kappa statistic.

We calculated the percentage of alerts in each rating category that the panelists rated high, medium or low, stratified by severity. We then used bivariate and step-wise multivariable linear regression analyses to examine the relationship between the rate at which clinicians accepted the drug interaction alert (independent variable) and the expert panel's mean rating of each attribute (dependent variable). Information about clinician acceptance of alerts was derived from the behaviour (i.e. accept or override an alerted prescription) of 2872 ambulatory clinicians in Massachusetts, Pennsylvania and New Jersey who used the PocketScript system to generate 229 663 electronic drug-drug interaction alerts in 2006. All analyses used Stata 9.0 (StataCorp, College Station, TX, USA). This study was reviewed in advance by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

Table I. Interrater reliability of characteristics of drug interaction alerts

Drug interaction attribute	Kappa statistic[a]
How would you rate the strength of scientific evidence for the interaction?	0.20
What is the estimated likelihood that interaction would result in an ADE requiring medical attention?	0.28
Does alert provide information that is already well known to the average PCP?	0.40
If an ADE resulted, how would you rate the severity of the typical event?	0.11
If an ADE resulted, how would you rate the severity of the most serious possible event?	0.16
Can PCPs readily act on the information?	0.13
Overall, does the interaction have value to the average PCP?	0.37

a Poor agreement = <0.20, fair agreement = 0.20–0.40, moderate agreement = 0.40–0.60, good agreement = 0.60–0.80 and very good agreement = 0.80–1.00.

ADE = adverse drug event; **PCP** = primary care provider.

Results

Interrater Reliability

Interrater reliability of the expert panel's judgements was fair at best (table I). Agreement was lowest for estimates regarding the severity of a typical or serious interaction, and whether clinicians could act on the information provided in the alert. Agreement was best for judgements about the familiarity of a primary care clinician with the interaction, and the overall assessment of the value of alert to the average primary care clinician (kappa = 0.37).

Expert Panel Ratings

Table II arrays the panelists' ratings of the 120 alerts, stratified by alert severity. In general, they judged that most low- and medium-severity alerts (as defined by Cerner Multum) were based on weak scientific evidence and would rarely lead to serious ADEs. They also judged that 95% of medium-severity and 90% of low-severity alerts are not valuable to the average PCP.

Panelists had more favourable ratings for high-severity alerts. Two-thirds of alerts were judged to have a moderate or strong evidence base and 30% of serious interaction alerts could 'sometimes' lead to an ADE requiring medical attention. Panelists judged that 44% of high-severity alerts would typically result in significant harm and 86% of high-severity alerts could result in a serious or life-threatening injury. They judged that all of the high-severity alerts were 'actionable' – the PCP could change their behaviour in order to act on the information provided in a high-severity alert. Overall, panelists judged that 71% of high-severity alerts probably or definitely had value to the average PCP.

Relationship between Clinicians' Acceptance of Alerts and Expert Panel Ratings

Of the 120 drug interaction alerts in our sample, the mean acceptance rate was 8.8% (SD 3.7%; range 0–23.1%).

When we examined the bivariate relationship between panelists' assessment of each drug interaction alert on the rate with which clinicians accepted the alert, we found many statistically significant relationships (table III). For example, a one category change (from weak to moderate or moderate to strong) in the strength of the scientific evidence for the interaction increased the rate

that clinicians accepted the alert by 2.3% (95% CI 1.1, 3.6). Given a baseline acceptance rate of 8.8%, a 2.3% increment equals a 26% relative change.

In the multivariable regression analysis, the decision of clinicians to accept drug interaction alerts increased (relative to a baseline alert acceptance rate of 8.8%) by 2.7% (95% CI 0.4, 5.1) for interactions that panelists judged would result in an ADE, by 2.3% (95% CI 0.9, 3.7) when PCPs lacked knowledge about the information presented in the alert and by 3.3% (95% CI 0.9, 5.8) when the PCP could readily act on the information provided in the alert. The overall value of the alert was dropped from the multivariable analysis since it was highly correlated with the other predictors.

Discussion

In order to examine the value of electronic drug interaction alerts to primary care clinicians, we recruited an expert panel to judge 120 alerts. Panelists assessed the scientific evidence, likelihood of an ADE, novelty of information to the clinician, severity of the typical and most serious possible event, ability of a clinician to act on the information and the overall value of the alert. The panel judged the value of high-severity alerts differently from that of moderate- and low-severity alerts in several important ways. High-severity alerts had a stronger scientific basis and a greater likelihood that the interaction would result in a

Table II. Summary of expert panel ratings of drug interaction alert attributes by severity

Drug interaction attribute	Alert severity			p-Value[a]
	high (%) [n = 80]	medium (%) [n = 20]	low (%) [n = 20]	
How would you rate the strength of scientific evidence for the interaction?				
weak	31	70	70	0.002
moderate	60	30	30	
strong	9	0	0	
What is the estimated likelihood that interaction would result in an ADE requiring medical attention?				
rarely	70	95	85	0.088
sometimes	29	5	15	
often	1	0	0	
Does alert provide information that is already well known to the average PCP?				
definitely or probably	51	25	50	0.121
probably not or definitely not	49	75	50	
If an ADE resulted, how would you rate the severity of the typical event?				
not harmful or minor/trivial	56	95	85	<0.001
significant	44	5	15	
serious or life threatening	0	0	0	
If an ADE resulted, how would you rate the severity of the most serious possible event?				
not harmful or minor/trivial	3	55	20	<0.001
significant	11	40	40	
serious or life threatening	86	5	40	
Can PCPs readily act on the information?				
definitely not or probably not	0	50	20	<0.001
probably or definitely	100	50	80	
Overall, does the interaction have value to the average PCP?				
definitely not or probably not	29	95	90	<0.001
probably or definitely	71	5	10	

a Fisher's exact test.

ADE = adverse drug event; **PCP** = primary care provider.

significant or serious ADE. Panelists judged that over two-thirds of high-severity alerts were useful to the PCP, compared with 5–10% of moderate- and low-severity alerts. In three States, the panel's clinical assessments were strongly associated with the observed behaviour of more than 2800 users of electronic prescribing. Clinicians in three States were more likely to accept the alerts (and abort or change a prescription) when the panel judged that the interaction would be likely to result in an ADE, when information about the interaction was not well known to the PCP and when clinicians could act on the information provided in the alert.

Electronic prescribing systems have been criticized for generating too many alerts of limited clinical utility.[4,11] We undertook this study to enable better understanding of the relationship between alert quality and alert acceptance decisions of practicing clinicians. As expected, we found a positive relationship between the expert panel's judgement of the value of the alert and the behaviour of clinicians. The value of the alert, as judged by the expert panel, had a substantial ability to predict behaviours of clinicians in acting to accept or override the alert; an incremental change in the perceived value of the alert by the expert panel translated into an absolute change of at least 2–3%, or a relative change of 20–30%.

Our study has implications for research and practice. Developers of alerts should permit practicing clinicians to review the alerts for their clinical value, and items that rank poorly should be suppressed. Interaction alerts for which there is low interrater reliability might be included in a manner that allows practitioners to suppress these alerts selectively, to fit their clinical practice style. In addition, modest interrater reliability within the expert panel suggests that some clinicians may find certain alerts useful, while other clinicians find the same alerts to be of limited use. Future research should attempt to identify groups of practitioners or practice settings that rate certain combinations of alerts most valuable. Developers should also create customizable systems to account for individual differences and preferences.

This study has several limitations, including fair to poor interrater reliability between the panelists' assessments. This finding is consistent with previous studies and is likely to be due to several factors.[12,13] Clinician familiarity with medication interactions may vary by duration of clinician experience and by the composition of a clinican's practice. Differences in judgements about alerts might also result from the weak quality of the evidence base, often confined to theoretical or

Table III. Relationship between decision of clinicians to accept drug interaction alert and expert panel rating of alert

Drug interaction attribute	Bivariate [OR (95% CI)]	Multivariable [OR (95% CI)][a]
How would you rate the strength of scientific evidence for the interaction? (1 = weak, 2 = moderate, 3 = strong)	2.34 (1.08, 3.60)	
What is the estimated likelihood that interaction would result in an ADE requiring medical attention? (1 = rarely, 2 = sometimes, 3 = often)	3.61 (1.82, 5.40)	2.73 (0.39, 5.06)
Does alert provide information that is already well known to the average PCP? (1 = definitely, 2 = probably, 3 = probably not, 4 = definitely not)	–0.56 (–1.78, 0.66)	2.32 (0.94, 3.69)
If an ADE resulted, how would you rate the severity of the typical event? (1 = not harmful, 2 = minor/trivial, 3 = significant, 4 = serious, 5 = life threatening)	3.30 (2.14, 4.47)	
If an ADE resulted, how would you rate the severity of the most serious possible event? (1 = not harmful, 2 = minor/trivial, 3 = significant, 4 = serious, 5 = life threatening)	1.91 (1.24, 2.59)	0.91 (–0.08, 1.89)
Can PCPs readily act on the information? (1 = definitely not, 2 = probably not, 3 = probably, 4 = definitely)	4.75 (3.13, 6.36)	3.34 (0.92, 5.75)
Overall, does the interaction have value to the average PCP? (1 = definitely not, 2 = probably not, 3 = probably, 4 = definitely)	3.18 (2.16, 4.20)	

a Step-wise linear regression model with backward elimination if $p < 0.2$.

ADE = adverse drug event; **PCP** = primary care provider; **OR** = odds ratio.

in vitro interactions, or to isolated case reports. These factors may be inherent limitations to our ability to create a set of alerts that most clinicians perceive as valuable.[14] Although we selected panelists based on their range of experience and expertise, a different set of reviewers might have interpreted the questions regarding each alert's value characteristics differently and therefore may have offered different judgements.

In addition, we examined alerts generated by one of two large commercial vendors of pharmaceutical decision support. Many commercial drug interaction alerts appear to be somewhat arbitrary, with relatively little agreement about the scientific basis of specific alerts. The generalizability of our results to other alert systems is uncertain. Finally, while the acceptance rate of alerts reflects the real-world behaviour of clinicians who use a commercial e-prescribing system in three States, it is possible that their decisions to accept or override alerts are idiosyncratic to the PocketScript system rather than to the alert itself. However, we believe that this is unlikely to seriously compromise the generalizablity of our findings since most e-prescribing systems share the common features required of prescription writing.

Conclusions

The value of electronic drug interaction alerts is influenced heavily by clinicians' judgements about the alert's clinical value. Using expert panel judgements on drug-drug interaction alerts may help to reduce the volume of alerts that have little clinical meaning. Given that clinicians have differing assessments about which alerts are valuable, developers should find ways to allow clinicians to suppress alerts selectively.

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