Randomized clinical trial of a customized electronic alert requiring an affirmative response compared to a control group receiving a commercial passive CPOE alert: NSAID—warfarin co-prescribing as a test case

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ABSTRACT

Background Studies that have looked at the effectiveness of computerized decision support systems to prevent drug—drug interactions have reported modest results because of low response by the providers to the automated alerts.

Objective To evaluate, within an inpatient computerized physician order entry (CPOE) system, the incremental effectiveness of an alert that required a response from the provider, intended as a stronger intervention to prevent concurrent orders of warfarin and non-steroidal anti-inflammatory drugs (NSAIDs).

Design Randomized clinical trial of 1963 clinicians assigned to either an intervention group receiving a customized electronic alert requiring affirmative response or a control group receiving a commercially available passive alert as part of the CPOE. The study duration was 2 August 2006 to 15 December 2007.

Measurements Alert adherence was compared between study groups.

Results The proportion of desired ordering responses (ie, not reordering the alert-triggering drug after firing) was lower in the intervention group (114/464 (25%) customized alerts issued) than in the control group (154/560 (28%) passive alerts firing). The adjusted OR of inappropriate ordering was 1.22 (95% CI 0.69 to 2.16).

Conclusion A customized CPOE alert that required a provider response had no effect in reducing concomitant prescribing of NSAIDs and warfarin beyond that of the commercially available passive alert received by the control group. New CPOE alerts cannot be assumed to be effective in improving prescribing, and need evaluation.

INTRODUCTION

Medication errors are a leading cause of death in American hospitals.1 Several studies have shown significant effects on medication errors with the use of computer-based reminders in an order entry system.2–4 However, the effect of computer-based advice in these studies is highly variable.5–14 and little is understood about the determinants of this variability. Recent studies have shown that computer-based recommendations for drug—drug interactions are overridden as much as 90% of the time.15–17 There are several characteristics of the alert itself that may affect the likelihood that the alert will be followed. Such factors as the nature of the alerted condition (eg, the perception by ordering clinicians that allergy alerts are more important than drug interaction alerts),18 19 how the alert integrates into clinical workflow (eg, an excessive volume of alerts interferes with workflow),20 and whether or not the alert is associated with a user’s action (eg, a drug interaction alert may not be relevant if the patient had previously received the alerted medication without complication)18 19 have all shown some impact on the likelihood that the advice will be followed.21 22 But a great many questions still remain on how to create the most effective tools for giving advice to practicing clinicians.

Commercial computerized provider order entry (CPOE) systems are commonly distributed with built-in programs that provide simple alerts to the providers. These simple alerts take the form of message boxes with a warning. The fact that many alerts may fire simultaneously reduces the likelihood that any individual alert will be followed. Since most alerts do not require an affirmative response by the prescriber, and this approach has been shown to be ineffective,6 the intervention in our study was a customized electronic alert that specifically tested the effectiveness of requiring clinicians to acknowledge the alert.

Warfarin management is complex because of the need for tight control of thromboplastins that determine the international normalized ratio (INR) and the many potential interactions between it and other drugs. There are so many potential interactions, in fact, that it is nearly impossible for physicians to remember all of them at any given time. Different drug interactions may have different propensities for causing adverse drug events of varying severity, but there is clear evidence that non-steroidal anti-inflammatory drugs (NSAIDs) given in conjunction with warfarin can increase bleeding risk by as much as fivefold compared to each drug alone.23 Most authors recommend generally avoiding NSAIDs when a patient is also receiving warfarin.24
A common attribute of alert designs that require physician response is that the computer window cannot be closed without forcing physicians to choose among several decision options. One study provided intervention physicians with a pop-up window with automated guideline reminders to order tests or treatments and required them to accept, reject, or modify the suggested guidelines. This study found improved adherence to recommended guidelines, although adherence declined over time. Another trial compared providers receiving computer reminders to perform screening tests and required to select a response (‘done/order today’, or ‘not applicable to this patient,’ or ‘patient refused,’ or ‘next visit’) to controls receiving similar reminders but without a required response. Again, more frequent compliance with reminders was seen among the intervention physicians. Another study activated and deactivated over a period of several weeks an automated decision support system delivering more conservative recommendations for psychotropic medications for hospitalized elderly patients. The intervention screen similarly required an explicit decision choice (‘change order to recommended medication’, ‘proceed with this order’, or ‘cancel this order’). The authors reported that prescriptions for every class of psychotropic drugs agreed with the system recommendations more frequently during the intervention periods.

An interesting study by Paterno et al. used inpatient alert log data to rank drug–drug interactions by severity and used several different displays to present this information to the clinicians. Serious alerts required clinicians either to cancel the order or discontinue a pre-existing drug order (‘hard stop alert’); less serious alerts also required action by the clinician, either to discontinue one of the drugs or to select an override reason; the least serious alerts were presented as information only, requiring no action of any kind from the clinician. Tiering the presentation of drug–drug interaction alerts by severity level was seen to be associated with higher rate of compliance for alerts leading the authors to conclude that how alerts are prioritized and presented to the user may be as important as which alerts to deliver.

In contrast, other studies did not find alerts to be effective—even those requiring the clinician’s response. In their study of the characteristics of drug allergy overrides in a hospital CPOE system that required the clinician to enter a free-text reason for the override, Hsieh et al. found that overrides were common. However, based on subsequent chart reviews, these overrides were mostly justified because of risk-benefit calculations for the particular patients. Similarly, in several Veterans Affairs medical centers, where entering a reason for the override is requested for critical drug–drug interactions, Grizzle et al. found that more than half of the responses provided no clinical justification for the override.

Thus, as noted earlier, alerts are effective in some domains and ineffective in others. A recent review by Eslami et al. and other reviews also show that the impact of CPOE systems is mixed. However, a majority of studies were not randomized, there were only a few studies specifically focused on alerts to prevent drug–drug interactions in the hospital setting, and the follow-up periods were too short to conclude that the effect was lasting.

**Research Question**

This study was designed to test the effectiveness of a customized CPOE alert specifically requesting a response by the provider using the NSAID–warfarin interaction as a model. This is a common, well-accepted, potentially serious drug interaction and, indeed, is one of the few that are. It also was occurring in our hospital, despite the presence of the conventional alert, suggesting the need to try something new.

**Methods**

**Study Setting**

The study was conducted at the Hospital of the University of Pennsylvania (HUP) and the Penn Presbyterian Medical Center (PMC) where all inpatient orders are entered using the Sunrise Clinical Manager (SCM, Eclipsys Corporation, Atlanta, Georgia, USA) CPOE system.

**Study Design**

The study was a randomized controlled trial of all 1865 resident physicians (RPs) and 98 nurse practitioners (NPs) involved in inpatient care. Attendings were not included as a unit of randomization since attendings at our hospitals do not normally enter the orders themselves; that is delegated to others.

The trial was active from 2 August 2006 to 15 December 2007. The study was approved by the University of Pennsylvania Committee on Studies Involving Human Beings, which waived the requirement for informed consent and HIPAA authorization.

**Study Groups**

**Intervention**

The alert was activated whenever a RP or NP placed an order for an NSAID with an already active warfarin order, if warfarin was started for a patient already on NSAIDs, or when ordering both simultaneously. The intervention in this study was a newly formatted alert that prompted the provider to discontinue the NSAID and order acetaminophen as an alternative. The specific text of the customized alert was:

‘Prescription of warfarin and NSAID together is contra-indicated.

Please select an alternative drug, such as acetaminophen, by clicking on View Actions button.’

The provider could then either click the ‘acknowledge’ button to continue with the order for a NSAID, or could click on the ‘view action’ button to discontinue the current order of a NSAID and start a new order for acetaminophen.

The control group received the standard passive alerts in the form of a message box warning the provider not to prescribe the combination drugs. A response was not required to allow the combination of drugs to be prescribed.

**Endpoints**

The primary outcome was a new concurrent prescription order for NSAIDs and warfarin accepted through the electronic ordering system. In this context, not reordering the alert-triggering drug within 10 minutes after the alert fired represented a desired clinical response.

**Data Collection**

The unit of analysis for this study was the alert that fired, or would have fired, whenever a prescription order for concurrent NSAID and warfarin was encountered during the inpatient stay. Alerts were attributed to the study group of the provider who ordered the second prescription—that is, the prescription that triggered the alert.

A 5-minute rule was applied to counting the total number of alerts, given that some alerts kept firing multiple times immediately one-after-another because providers, despite the customized alert, attempted to re-enter the order for the triggering
medication to ensure that the order was processed. Accordingly, alerts firing within ≤5 minutes of each other were counted as a single episode, whereas alerts firing within >5 minutes of each other were counted as separate episodes.

If the alert-triggering drug was not reordered within an interval of 10 minutes after the alert fired, it was counted as a ‘desired clinical response’ (ie, not having active concurrent orders for warfarin and NSAID after the alert had fired). As a secondary analysis, we also investigated a 24-hour interval after alert firing.

**Statistical analysis**

‘Desired ordering rates’ in the intervention and control groups were compared using logistic regression, accounting also for resident physician and nurse practitioner clustering (ie, the non-independence of outcomes in patients within the same provider), using STATA 10.

**RESULTS**

Figure 1 shows the subject randomization flow, including the 1963 providers in the analysis (960 intervention providers receiving the customized alerts and 1003 control providers receiving the standard-of-care alerts). Overall there were 1218 alerts. After applying the 5-minute rule (namely, counting as a single alert that fired within ≤5 minutes of each other), there were 1024 alerts: 464 in the intervention group and 560 in the control group.

The proportion of desired ordering responses (ie, not reordering the alert-triggering drug within 10 minutes of firing) was lower in the intervention group (25% (114/464) customized alerts issued) than in the control group (28% (154/560) passive alerts firing). The odds of inappropriate ordering by the intervention providers was adjusted OR 1.22 (95% CI 0.69 to 2.16; p=0.48), indicating that the modified alert had failed to prevent the concomitant ordering of warfarin and NSAIDs (see table 1).

These results were adjusted for provider type (RP or NP) and for hospital (HUP or FMC) as potential confounders and accounting for clustering by provider (ie, adjusting for the non-independence of outcomes in patients within the same provider). It is of interest to note the high mean number of alerts per provider (3.5 vs 4.5 in the intervention and control groups, respectively) even after counting alerts triggered by repeated orders within ≤5 minutes as a single alert event. The 25th, 50th, and 75th percentiles of the number of alerts triggered by offending orders per provider were 1, 2, and 4, respectively, in each group.

The results from the secondary analysis based on behavior within 24 hour after an alert had fired were not substantively different and are not presented.

There was a trend over the 17-month study period with decreasing proportion of desired ordering responses over time (OR 1.09 per month; p=0.007). There was also a significant month-by-study group interaction (p=0.04). The interaction was the result of multiple crossovers in the desired ordering rates between the two groups over time. Overall, there was no group difference.

**DISCUSSION**

We observed in a randomized clinical trial that a customized CPOE alert that required a provider response had no effect in reducing concomitant prescribing of NSAIDs and warfarin beyond that of the commercially available passive alert received by the control group.

To date, most studies that looked at the effectiveness of computerized decision support systems designed in particular to reduce medication errors of drug–drug interactions have reported only modest results. Providers tend to override the alerts because they are perceived to be non-specific, lacking the providers’ additional knowledge of the clinical situation for the specific patient context.

One area for further research is the best way to display alerts to providers to make drug alerts more effective and reduce overriding. If alerts are ineffective because they are easy to ignore, then attention should be given to finding ways to amplify the effect of the alert. We focused on one feature of such displays—namely, the requirement that providers acknowledge the alert as compared to not requiring any active response. We found that this feature in itself as part of a computerized order entry system was not sufficient. The customized alert advising the clinician to order acetaminophen instead of NSAID in patients requiring warfarin and to acknowledge the alert was no more effective than the standard of care passive alert in reducing the undesired prescribing.

On the other hand, requiring more interaction from clinicians when alerts fire, in order to increase compliance, may be disruptive to the workflow and may have other unintended consequences. A recent trial by Strom et al to evaluate the effectiveness of a nearly ‘hard stop’ CPOE prescribing alert intended to reduce concomitant orders of warfarin and trimethoprim/sulfamethoxazole found it to be extremely effective in changing prescribing. However, this intervention precipitated treatment delays among patients in the intervention group needing immediate drug treatment, leading to early termination.
Thus, it potential confounders that may have in the study groups was a concurrent comparison regardless. Thus, the comparison between joining the study population and old house-staff leaving the study. It is common for RPs and NPs to discuss the care plan of patients, which include issues of ordering medications. More¬

Another limitation is that because the study took place over 15 months, all residents did not participate in the study for the same amount of time. Fluctuations in the effectiveness of the order system menu can be varied by individual user. In addition, we wanted to keep each practitioner in the same study group for the duration of the study to reduce contamination between the two groups. An additional strength is the large number of clinicians included in the study (approximately 2000).

of the study. Of course, given our current results do not indicate that this additional burden on physicians leads to additional effectiveness, that too argues not to implement such alerts.

The strength of this study was its randomized design. The decision to randomize clinicians rather than patients was moti¬

The customized alert may have been too similar to the alert in the control group, although we do not think so, since our alert provided an alternative strategy and forced a response. The customized alert may have been flawed if it led to misunder¬

In conclusion, a customized CPOE alert that required a provider response had no effect in reducing concomitant prescribing of NSAIDs and warfarin beyond that of usual standard of care. CPOE alerts cannot be assumed to be effective in improving prescribing and need to be formally evaluated.

Table 1 Frequency of alerts for warfarin and non-steroidal anti-inflammatory drugs (NSAIDs) that were followed by desired response by study group

<table>
<thead>
<tr>
<th>Study group</th>
<th>Total alerts fired* (alerts triggered by concurrent ordering of warfarin and NSAID)</th>
<th>Desired ordering responses (proportion of the alerts that were followed by an appropriate action (ie, the alert-triggering drug was not reordered within 10 min after the alert fired))</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR† (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Intervention</td>
<td>464</td>
<td>114 (25%)</td>
<td>1.16 (0.88 to 1.54)</td>
<td>1.22 (0.69 to 2.16)</td>
</tr>
<tr>
<td>Control group</td>
<td>560</td>
<td>154 (28%)</td>
<td></td>
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*Counting as a single event alerts that were fired within ≤5 minutes of each other.
† Adjusted for study group, hospital, provider type, and clustering by provider type.

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REFERENCES


