PART III. PATIENT SAFETY PRACTICES & TARGETS

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Section A. Adverse Drug Events (ADEs)

Chapter 6. Computerized Physician Order Entry (CPOE) with Clinical Decision Support Systems (CDSSs)

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Background

Medication errors and *adverse drug events* (ADEs) are common, costly, and clinically important problems.[1-7] Two inpatient studies, one in adults and one in pediatrics, have found that about half of medication errors occur at the stage of drug ordering,[2, 7] although direct observation studies have indicated that many errors also occur at the administration stage.[8] The principal types of medication errors, apart from missing a dose, include incorrect medication dose, frequency, or route.[2] ADEs are injuries that result from the use of a drug. Systems-based analysis of medication errors and ADEs suggest that changes in the medication ordering system, including the introduction of *computerized physician order entry* (CPOE) with *clinical decision support systems* (CDSSs), may reduce medication-related errors.[9]

Despite growing evidence and public mandates, implementation of CPOE has been limited. The Leapfrog Group, a consortium of companies from the Business Roundtable, has endorsed CPOE in hospitals as one of the 3 changes that would most improve patient safety in America (see also Chapter 55).[10] A Medicare Payment Advisory Commission report suggested instituting financial incentives for CPOE implementation.[11] US Senators Bob Graham (D-Fla.) and Olympia Snowe (R-Maine) recently introduced a bill, entitled the "Medication Errors Reduction Act of 2001," to establish an informatics system grant program for hospitals and skilled nursing facilities.[12] In addition, California recently enacted legislation stipulating that acute care hospitals implement information technology, such as CPOE to reduce medication-related errors.[13]

Practice Description

CPOE refers to a variety of computer-based systems of ordering medications, which share the common features of automating the medication ordering process. Basic CPOE ensures standardized, legible, complete orders by only accepting typed orders in a standard and complete format. Almost all CPOE systems include or interface with CDSSs of varying sophistication. Basic clinical decision support may include suggestions or default values for drug doses, routes, and frequencies. More sophisticated CDSSs can perform drug allergy checks, drug-laboratory value checks, drug-drug interaction checks, in addition to providing reminders about corollary orders (eg, prompting the user to order glucose checks after ordering insulin) or drug guidelines to the physician at the time of drug ordering (see also Chapter 53).

At times, CDSSs are implemented without CPOE. Isolated CDSSs can provide advice on drug selection, dosages, and duration. More refined CDSSs can incorporate patient-specific information (for example recommending appropriate anticoagulation regimens), or incorporate pathogen-specific information such as suggesting appropriate anti-infective regimens. After viewing such advice, the physician proceeds with a conventional handwritten medication order.

Prevalence and Severity of the Target Safety Problem

It is estimated that over 770,000 people are injured or die in hospitals from ADEs annually.[4, 5, 14] The few hospitals that have studied incidence rates of ADEs have documented rates ranging from 2 to 7 per 100 admissions.[2, 4, 15, 16] A precise national estimate is difficult to calculate due to the variety of criteria and definitions used by researchers.[17] One study of preventable inpatient ADEs in adults demonstrated that 56% occurred at the stage of ordering, 34% at administration, 6% at transcribing, and 4% at dispensing.[2] In this study, the drug class most commonly associated with preventable ADEs was analgesics, followed by sedatives and antibiotics. Even fewer studies have been conducted in the outpatient setting. One recent cross-sectional chart review and patient care survey found an ADE rate of 3% in adult primary care outpatients.[18]

Opportunities for Impact

Clear data do not exist about the prevalence of CPOE with CDSSs or isolated CDSSs. One survey of 668 hospitals indicated that 15% had at least partially implemented CPOE.[19] A slightly more recent survey of pharmacy directors at 1050 acute care hospitals in the United States (51% response rate) reported that 13% of hospitals had an electronic medication order-entry system in place, while an additional 27% stated they were in the process of obtaining such a sysytem.[20]

Study Designs

The 4 studies listed in Table 6.1 evaluated CPOE with CDSSs.[21-24] The first study, a randomized controlled trial evaluating the utility of CPOE in improving prescribing for corollary orders, was conducted by the Regenstrief Institute for Health Care (affiliated with the Indiana University School of Medicine).[21] The remaining 3 studies evaluated the CPOE system at Brigham and Women's Hospital (BWH).[22-24] Of note, both the Regenstrief and BWH systems are "home-grown" rather than "off-the-shelf" commercial systems. The first BWH study was a cross-sectional analysis comparing an intervention period of CPOE with CDSSs for adult inpatients on medical, surgical, and intensive care wards with a historical period.[22] The other 2 BWH studies were time series analyses of orders written for adult inpatients.[23, 24]

Table 6.2 lists 4 studies[25-28] that evaluated isolated CDSSs, 2 of which represent systematic reviews.[25, 26] Hunt et al[25] updated an earlier systematic review,[29] and included 68 studies that prospectively evaluated use of CDSSs in a clinical setting by a healthcare practitioner with a concurrent control. Importantly, Hunt et al included studies of outpatient settings in their review. Walton's review addressed 15 articles that studied computerized advice on drug dosage for inpatients.[26] Evans et al, at Latter Day Saints Hospital, performed the other 2 studies,[27, 28] again on a "home-grown" system. The first was a randomized controlled trial of empiric antibiotic selection using CDSSs.[27] The second study was a cross-sectional analysis comparing an intervention period of a computer-assisted management program for anti-infectives with a historical control period.[28] This second study[28] was likely excluded from the systematic review by Hunt et al[25] for methodologic reasons, as it did not have a concurrent control. The reasons for excluding the first study[27] remain unclear. Finally, it is important to emphasize again that of the primary studies that were included, 6 of 8 were performed at 3 institutions with sophisticated "home-grown" systems.

Study Outcomes

Adverse drug events (ADEs), (injuries that result from the use of drugs) by definition constitute clinical outcomes (Level 1). ADEs that are associated with a medication error are considered preventable, while those not associated with a medication error (eg, known medication side effects) are considered non-preventable. An example of a preventable ADE is the development of rash after the administration of ampicillin to a known penicillin-allergic patient. In contrast, a non-preventable ADE would be development of an ampicillin-associated rash in a patient with no known drug allergies. Non-intercepted serious medication errors include non-intercepted potential ADEs and preventable ADEs (ie, medication errors that either have the potential or actually cause harm to a patient).

Medication errors refer to errors in the processes of ordering, transcribing, dispensing, administering, or monitoring medications, irrespective of the outcome (ie, injury to the patient). One example is an order written for amoxicillin without a route of administration. Other medication errors have a greater potential for patient harm and so are often designated as "serious medication errors" or "potential ADEs" – eg, an order for amoxicillin in a patient with past anaphylaxis to penicillin.

Potential ADEs may or may not be intercepted before reaching the patient. An example of an intercepted potential ADE would be an order written for an acetaminophen overdose that is intercepted and corrected by a nurse before reaching the patient. An example of a non-intercepted potential ADE would be an administered overdose of acetaminophen to a patient who did not suffer any sequelae.

Medication errors include a mixture of serious medication errors with a significant potential for patient injury (Level 2) and other deviations from recommended practice that do not have a clear or established connection to adverse events (Level 3). Examples of the latter include failure to choose the optimal dosing schedule for a medication and many standards related to monitoring serum drug levels and routine electrolytes.

Only 2 studies (from a single institution) evaluating CPOE with CDSSs included ADEs as a secondary outcome (Level 1),[22] and even these studies primary outcomes were serious medication errors (Level 2) and non-intercepted medication errors.[23] The other studies reported a variety of other errors often involving mixtures of Level 2 and Level 3 outcomes – eg, "prescribing practices"[24] and "corollary orders."[21] *Corollary orders* refer to orders required to detect or ameliorate adverse reactions that may result from the trigger order - eg, checking the serum creatinine a minimum of 2 times per week in a patient receiving a nephrotoxic agent such as amphotericin. Many corollary orders capture Level 3 outcomes, as failure to prescribe these orders would in most cases have no clear impact on clinical outcomes – eg, failure to order daily tests for fecal occult blood in patients on heparin or screening audiometry for patients receiving vancomycin.[21]

The predominance of Level 2 and 3 outcomes in these studies is understandable, given the much higher frequency of these outcomes compared to actual ADEs and the enormous costs of conducting these studies.

Similarly, the studies evaluating CDSSs reported a mixture of outcomes from Levels 1-3. Hunt et al reviewed articles to determine changes in patient outcomes (Level 1) or physician performance (Levels 2 and 3, depending on the practice).[25] Walton et al evaluated a range of outcomes (Levels 1-3), including reductions in "adverse reactions and unwanted effects" (Level 1).[26] In one study, Evans et al determined rates of pathogen susceptibility to an antibiotic

regimen[27] (Level 2); another study by the same authors evaluated adverse drug events caused by anti-infectives as a main outcome (Level 1).[28]

Evidence for Effectiveness of the Practice

Of the 2 studies at BWH that addressed the impact of CPOE with CDSSs on medication errors and ADEs, the first demonstrated a 55% decrease in serious medication errors.[22] As a secondary outcome, this study found a 17% decrease in preventable ADEs, which was not statistically significant. The second study, a time series analysis, demonstrated marked reductions in all medication errors excluding missed dose errors and in non-intercepted serious medication errors.[23] The number of ADEs in this study was quite small – 25 in the baseline period and 18 in the third of the 3 periods with CPOE and CDSS. Correcting for the number of opportunities for errors, the total number of ADEs/1000 patient days decreased from 14.7 to 9.6 ($p=0.09$). For the sub-category of preventable ADEs, the reduction (from 5 to 2) achieved borderline statistical significance ($p=0.05$).

Overhage et al and Teich et al studied more focused aspects of the medication system. Overhage et al[21] studied computerized reminders for corollary orders (eg, entering a laboratory order to check electrolytes when ordering potassium for a patient) and showed a greater than 100% improvement in the rate of corollary orders ($p<0.0001$). Teich et al[24] studied a broad range of computerized clinical decision support tools utilized at BWH and demonstrated 5 prescribing improvements in types, doses, and frequencies of drug usage.

In summary, these studies provide some evidence that CPOE with CDSSs can substantially decrease medication errors in broad as well as in more focused areas. Despite the significant impact on medication errors, the reduction in ADEs did not achieve statistical significance in one study,[22] and achieved only borderline significance in one of the outcomes in the other study.[23] Furthermore, the systems evaluated in this relatively small literature were developed internally rather than purchased and installed, so the potential impact of commercially available systems remains somewhat speculative.

In the studies evaluating CDSSs, 2 were systematic reviews.[25, 26] In Hunt's review, which emphasized clinical performance, 6 of 14 studies reported improvements in patient outcomes and 43 of 65 studies showed improvement in physician performance.[25] This study concludes that CDSSs can enhance clinical performance for drug dosing, preventive care, and other aspects of medical care, but that the impact of CDSSs on patient outcomes remains unclear (see also Chapter 53). Walton's systematic review evaluated computerized drug dosage advice and found a 6% decrease in adverse drug reactions.[26] The authors concluded that there is some limited evidence that CDSSs for drug dosing are effective, however there are relatively few studies, many of which are of sub-optimal quality. They also suggest that further research is needed to determine if the CDSS benefits realized with specialist applications can be realized by generalist use. Evans et al performed the remaining 2 studies.[27, 28] The 1994 study evaluated the use of a computerized antibiotic selection consultant, and demonstrated a 17% greater pathogen susceptibility to an antibiotic regimen suggested by a computer consultant versus a physician ($p<0.001$).[27] The second study demonstrated a 70% decrease in ADEs caused by anti-infectives ($p=0.018$) through use of a computer based anti-infective management program. As with CPOE, these CDSSs studies demonstrate improvements in medication errors with statistical significance. In addition, both Walton's systematic review[26] and the latter study by Evans et al[28] demonstrated significant decreases in ADEs. Importantly, each of these CDSSs studies only addressed focal aspects of the medication system. In addition, relatively little information is available about the differences between systems.

Potential for Harm

Faulty decision support data, for example an incorrect default dosing suggestion, can lead to inappropriate ordering choices by physicians. The BWH time series analysis demonstrated an initial rise in intercepted potential ADEs due to the structure of the ordering screen for potassium chloride.[23] This structural error was identified and easily rectified, but underscores the importance of close scrutiny of all aspects of CPOE screens, both initially and on an ongoing basis.[23]

Also, analogously to writing an order in the wrong patient chart in a conventional system, a physician can electronically write an order in the wrong patient's record - eg, after walking away from the terminal, opening the wrong record from a personalized rounding list. In addition, it is critical that the trigger level for warnings appropriately balances alarm sensitivity and specificity. These systems must have thresholds set so that physicians receive warnings in situations with a potential for significant harm, without being overwhelmed by "false alarms." Another potential risk is hardware outage or software instability. For example, the reliability that is needed with CPOE is much higher than that required for systems that simply report laboratory results.

Costs and Implementation

Six of the studies described in this review evaluated "home-grown" rather than "off-the-shelf" systems. The present costs for purchasing commercial systems are substantially more than the previous costs of developing such systems. For BWH, the cost of developing and implementing CPOE in 1992 was estimated to be $1.9 million, with maintenance costs of $500,000 per year. In comparison, the cost of purchasing and implementing large commercial systems varies substantially, but may be on the order of tens of millions of dollars. Several studies demonstrate that only minimal resources are needed to introduce and/or maintain decision support programs into existing order entry programs.[21, 24, 30]

Relatively few data are available regarding the financial benefits of CPOE, although they extend well beyond medication-related events. The net savings of the BWH system are estimated at $5-10 million per year.[31] It is estimated that the costs to BWH for preventable ADEs are $2.8 million annually.[32] Evans et al reported a $100,000 per year cost avoidance with a computer-assisted antibiotic dosing program largely attributable to decreased antibiotic use and avoided ADEs.[33]

Importantly, healthcare systems must garner both financial and organizational support before introducing CPOE with CDSSs. CPOE requires a very large up-front investment with more remote, albeit substantial returns. In addition, CPOE impacts clinicians and workflow substantially. Its complexity requires close integration with multiple systems, such as the laboratory and pharmacy systems. Failure to attend to the impact of such a large-scale effort on organizational culture and dynamics may result in implementation failure.[34] Therefore, it is essential to have organizational support and integration for its successful implementation and use.

Comment

The literature supports CPOE's beneficial effect in reducing the frequency of a range of medication errors, including serious errors with the potential for harm. Fewer data are available regarding the impact of CPOE on ADEs, with no study showing a significant decrease in actual patient harm. Similarly, isolated CDSSs appear to prevent a range of medication errors, but with

few data describing reductions in ADEs or improvements in other clinical outcomes. Finally, the studied CDSSs address focused medication use (for example, antibiotic dosing) rather than more general aspects of medication use.

Further research should be conducted to compare the various types of systems and to compare "home-grown" with commercially available systems. Such comparisons are particularly important since the institutions that have published CPOE outcomes have generally been those with strong institutional commitments to their systems. Whether less committed institutions purchasing "off the shelf" systems will see benefits comparable to those enjoyed by "pioneers" with home-grown systems remains to be determined. Studying the benefits of such complex systems requires rigorous methodology and sufficient size to provide the power to study ADEs. Further research also needs to address optimal ways for institutions to acquire and implement computerized ordering systems.

Table 6.1. Studies of computerized physician order entry (CPOE) with clinical decision support systems (CDSSs)[*]

Study	Study Design	Study Outcomes	Results
Overhage, 1997.[21] Impact of faculty and physician reminders (using CPOE) on corollary orders for adult inpatients in a general medical ward at a public teaching hospital affiliated with the Indiana University School of Medicine	Level 1 (RCT with physicians randomized to receive reminders or not)	Levels 2 & 3 (errors of omission in corollary orders)	25% improvement in ordering of corollary medications by faculty and residents ($p<0.0001$)
Bates, 1998.[22] CPOE with CDSSs for adult inpatients on medical, surgical, and intensive care wards at BWH, a tertiary care center affiliated with Harvard University	Levels 2 & 3 (two study designs)	Level 1 (ADE rates) and Level 2 (serious medication errors)	55% decrease in non-intercepted serious medication errors ($p=0.01$) 17% decrease in preventable ADEs ($p=0.37$)
Bates, 1999.[23] CPOE with CDSSs for adult inpatients in 3 medical units at BWH	Level 3 (retrospective time series)	Level 1 (ADEs) and Level 2 (main outcome measure was medication errors)	81% decrease in medication errors ($p<0.0001$) 86% decrease in non-intercepted serious medication errors ($p=0.0003$)
Teich, 2000.[24] CPOE with CDSSs for all adult inpatients at BWH	Level 3 (retrospective before-after analysis)	Levels 2 & 3 (changes in 5 prescribing practices)	Improvement in 5 prescribing practices ($p<0.001$ for each of the 5 comparisons)

[*] ADE indicates adverse drug event; BWH, Brigham and Women's Hospital; and RCT, randomized controlled trial.

Table 6.2. Studies of clinical decision support systems (CDSSs)*

Study Setting	Study Design	Study Outcomes	Results
Hunt, 1998.[25] Use of CDSSs by healthcare practitioners in multiple inpatient and outpatient settings	Level 1A (systematic review of RCTs)	Levels 1 & 2 (a variety of measures related to patient outcomes and physician practice, not just ADEs and processes of care related to medication use.	6 of 14 studies showed improvement in patient outcomes 43 of 65 studies showed improvement in physician performance
Walton, 2001.[26] Use of CDSSs for drug dosage advice by healthcare practitioners for 1229 patients in multiple inpatient settings	Levels 1A-3A (systematic review of RCTs, interrupted time series analyses, and controlled before-after studies)	Level 1 (one main outcome measure was adverse drug reactions	Absolute risk reduction with CDSSs: 6% (95% CI: 0-12%)
Evans, 1994.[27] Use of a computerized antibiotic selection consultant for 451 inpatients at Salt Lake City's LDS Hospital, a 520-bed community teaching hospital and tertiary referral center	Level 1 (RCT with crossover design)	Level 2 (one of 5 primary outcomes was pathogen susceptibility to prescribed antibiotic regimens	17% greater pathogen susceptibility to an antibiotic regimen suggested by computer consultant versus physicians ($p<0.001$)
Evans, 1998.[28] Computer-based anti-infective management program for 1136 intensive care unit patients from a 12-bed ICU at LDS Hospital	Level 2 (prospective before-after analysis)	Level 2 (one primary outcome was ADEs due to anti-infective agents	70% decrease in ADEs caused by anti-infectives ($p=0.02$)

* ADE indicates adverse drug event; CI, confidence interval; ICU, intensive care unit; and RCT, randomized controlled trial.

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