Implementation of a Clinical Decision Support System for Computerized Drug Prescription Entries in a Large Tertiary Care Hospital

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ABSTRACT: **Background:** Prescription errors are common in hospitalized patients and result in significant morbidity, mortality and costs. Electronic prescriptions with computerized physician order entry systems (CPOE) and integrated computerized decision support systems (CDSS providing online alerts) reduce prescription errors by approximately 50%. However, the introduction of CDSS is often met by opposition due to the flood of alerts, and most prescribers eventually ignore even crucial alerts ("alert fatigue").

Objectives: To describe the implementation and customization of a commercial CDSS (SafeRx®) for electronic prescribing in Internal Medicine departments at a tertiary care center, with the purpose of improving comprehensibility and substantially reducing the number of alerts to minimize alert fatigue.

Methods: A multidisciplinary expert committee was authorized by the hospital administration to customize the CDSS according to the needs of six internal medicine departments at Sheba Medical Center. We assessed volume of prescriptions and alert types during the period February–August 2012 using the statistical functions provided by the CDSS.

Results: A mean of 339 ± 13 patients per month per department received 11.2 ± 0.5 prescriptions per patient, 30.1% of which triggered one or more CDSS alerts, most commonly drug-drug interactions (43.2%) and dosing alerts (38.3%). The review committee silenced or modified 3981 alerts, enhancing comprehensibility, and providing dosing instructions adjusted to the patient's renal function and recommendations for follow-up.

Conclusions: The large volume of drug prescriptions in internal medicine departments is associated with a significant rate of potential prescription errors. To ensure its effectiveness and minimize alert fatigue, continuous customization of the CDSS to the specific needs of particular departments is required.

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KEY WORDS: drug safety, prescription errors, computerized decision support system (CDSS), computerized physician order entry (CPOE), alert fatigue

Since the Institute of Medicine's 2000 consensus report "To err is human" [1], medication errors and resulting adverse drug effects have become an increasing concern for both health care providers and the public. Medication errors are common in hospitalized patients, estimated to occur on average once a day in every hospitalized patient [2]. Importantly, medication errors and resultant adverse drug events are associated with significant morbidity, mortality and costs [3,4], namely, more than a doubling of the duration of hospitalization and incurred costs [5]. In fact, the annual in-hospital costs associated with preventable adverse drug events in a 700-bed teaching hospital was estimated in 1993 to amount to $2.8 million, the equivalent of 4.3 million in 2006 dollars [3].

Prescription errors are the most common medication errors [6] and include, for example, incorrect medication dosage and frequency, ignoring potentially significant drug-drug interactions, inadequate dose adjustment for renal or hepatic function, and inadvertent omission of required medications [7]. Approximately 7–15% of hospital medication prescriptions include an error, and about 30–50% of hospitalized patients are exposed to at least one prescription error during hospitalization [8,9]. Electronic prescriptions, implemented as computerized physician order entry systems, were recently introduced to reduce the risk of prescription errors, particularly when associated with clinical decision

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support systems [7,10]. Indeed, a recent meta-analysis estimated that CPOE systems reduce medication errors by 48% (95% confidence interval 41–55%) [11].

Although these systems reduce the rate of prescription errors, their acceptance among physicians has been variable: CDSS cause interruption and delay in the workflow, frequently result in "alert fatigue" because of a flood of alerts of little clinical relevance, and often give alerts without providing therapeutic alternatives or specific instructions [12-14]. Moreover, the impact of CPOE/CDSS systems on clinical outcomes, i.e., the rate of adverse drug effects, has not yet been clearly established, partly because most studies were not sufficiently powered [14,15]. Yet the use of advanced health information technology, including CPOE systems with CDSS, has been strongly supported by regulatory bodies such as the U.S. Health Information Policy Committee, with substantial financial incentives for hospitals that implement these technologies [2].

There is little information about medication errors in Israeli hospitals. Extrapolating from small studies, the medication error rates appear to be comparable to those in other western countries, ranging from 3% to 36% [16-19], depending on the definition of medication error. Following the example of U.S. and European regulators [2], the Israel Ministry of Health recently required the stepwise implementation of electronic medical records and CPOE systems in hospitals between the years 2013 and 2015 and recommended the use of integrated CDSS [20].

At the Sheba Medical Center (www.sheba.co.il), electronic medical records and CPOE systems were introduced in 2001 and then upgraded in 2007 (Chameleon™, Elad Healthcare Solutions, Tel Aviv, Israel). In addition, starting in 2011, a commercial drug prescription CDSS was introduced. This manuscript describes the implementation and customization of a drug prescription CDSS in a large tertiary care hospital.

MATERIALS AND METHODS

DESCRIPTION OF THE DRUG PRESCRIPTION CDSS

SafeRx® (Clinicode Healthcare IT Solutions Ltd., Tel Aviv, Israel) is a commercial clinical decision support system that can be implemented within any available electronic medical record using a CPOE system. When a drug prescription is entered, the system provides real-time alerts to the physicians, presented as a pop-up window on the computer screen. The physician can then either change the prescription or override the alert, choosing a specific reason from a pull-down menu. The system's drug database is based on different sources of information, including the physician's package insert and commercial drug information databases (e.g., Lexi-Comp®, Hudson, OH, USA; Micromedex®, Truven Health Analytics, Ann Arbor, MI, USA).

ALERT TYPES

- *Dose alerts* are triggered if a drug prescription deviates from the recommended range for single doses, daily doses, dose rates (for infusions), or dosing intervals.
- *Renal dose adjustments alerts* in patients with decreased renal function are triggered for drugs for which dosing depends on renal function. The CDSS calculates the estimated glomerular filtration rate using the Cockgroft-Gault based on the latest serum creatinine concentration and body weight imported from the EMR. The CDSS presents ranges for recommended single doses and dosing intervals specifically for the given eGFR.
- *Drug-drug interaction alerts* are triggered if the active ingredient in the new prescription is listed as potentially interacting with any of the concomitant drugs listed in the patient's EMR. Drug-drug interaction alerts are classified by clinical severity levels (mild, moderate, or major).
- *Duplicate therapy alerts* are triggered if the newly prescribed drug belongs to the same therapeutic class as a concomitant drug in the patient's EMR. These alerts are intended to prevent therapeutic redundancy, e.g., the concomitant treatment with two or more benzodiazepine drugs or beta-blockers.

SYSTEM REVIEW AND ADJUSTABILITY

All alerts are saved and can be reviewed by the system administrator. The SafeRx CDSS allows for system adjustments by the administrator according to the institution's specific needs. Any definition in the system's database – e.g., dose recommendations – as well as the phrasing of the alerts, can be changed. Additionally, the system administrator may choose to present or suppress specific alerts or alert types, and these choices can be individualized for specific hospital departments.

IMPLEMENTATION AND CUSTOMIZATION

At the Sheba Medical Center, SafeRx was introduced as a pilot project in internal medicine departments starting in January 2011. An expert review committee consisting of two clinical pharmacologists and a pharmacist (Y.Z., D.K., R.L.) was authorized by the hospital administration to review and customize the alerts. On implementation in a new department, the CDSS was operated in "silent mode" during the first weeks, i.e., without presenting the alerts to the prescribing physician. During this phase the review committee assessed the types and frequencies of different alerts and modified and silenced alerts accordingly. Then, the CDSS was operated in "active mode," presenting the alerts to the prescribing physician. The review committee continued reviewing the alerts on a regular basis, receiving comments from the clinical departments and adjusting alerts and their triggers accordingly. The main goals of the adjustments were: a) to substantially reduce

CPOE = computerized physician order entry systems
CDSS = clinical decision support systems
EMR = electronic medical record
eGFR = estimated glomerular filtration rate

the number of alerts in order to minimize alert fatigue, and b) to rephrase alerts to improve comprehensibility.

CDSS ALERT VOLUME

For a preliminary quantitative analysis of prescription volume and medication alerts by the CDSS, we used the SafeRx® statistical tools to examine alerts triggered by medical prescriptions in six internal medicine departments during the months February–April and June–August 2012. These departments each have 36–43 hospitalization beds, including a 5-bed step-down intensive care unit in most departments.

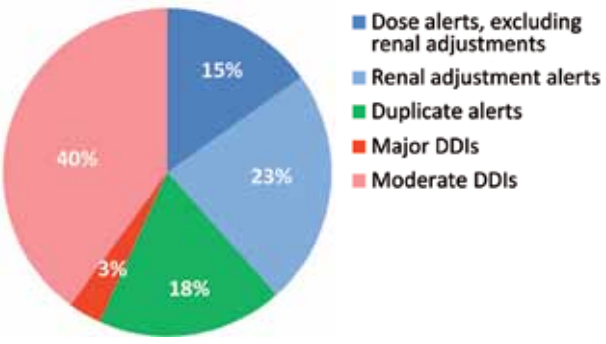
This study was approved by the Sheba Medical Center Institutional Review Board, which waived the requirement of informed consent contingent on de-identified data analysis.

RESULTS

CDSS ALERT VOLUME

During the 6 month observation period, 12,189 patients were hospitalized in the six internal medicine departments studied and received 136,459 medication prescriptions. A mean (± SD) of 339 ± 13 patients were hospitalized per department each month, receiving 3791 ± 201 prescriptions, corresponding to 11.2 ± 0.5 prescriptions per patient. Among these, 1140 ± 70 prescriptions (30.1%) triggered one or more CDSS alerts each month, for a total of 1408 ± 82 monthly alerts per department. Thus, during the hospitalization (mean duration 3.5 ± 0.6 days), the average patient received 4.2 ± 0.2 alerts, approximately one alert per hospitalization day. The most common alert types were drug interactions (43.2%), 3.3% of which were classified as major, and dosing alerts (38.3%), mostly (60.6%) alerts about doses inappropriate for the patient's renal function [Figure 1].

Figure 1. Distribution of alert types triggered by electronic prescriptions in internal medicine departments. During a 6 month period in six internal medicine departments 136,459 prescriptions triggered a total of 50,696 alerts



DDI = drug-drug interaction

CDSS CUSTOMIZATION

Drug-drug interactions of minor clinical relevance are common, rarely result in patient harm, and are usually overridden by the prescriber. We therefore decided at the implementation stage to silence all drug-drug interaction alerts of minor clinical significance. In addition, between January 2011 and August 2012, we silenced or modified a total of 3981 alerts. We used the following criteria to silence specific alerts:

- **Drug interactions:** If there was poor evidence (case reports or in vitro studies only), the magnitude or clinical significance of the effect was considered small, especially at the doses commonly used (e.g., codeine enhancing blood pressure-lowering effect of angiotensin receptor blocker drugs), the reported clinical outcome was not potentially serious (e.g., eplerenone and sertraline: decreased eplerenone clearance due to competitive inhibition of CYP3A4-mediated metabolism by sertraline), or the combination of the two drugs was common in clinical practice (e.g., concomitant use of warfarin and aspirin). Table 1 lists additional examples.
- **Duplicate therapy:** If two drugs are commonly prescribed concomitantly to achieve additive pharmacodynamic response (e.g., furosemide and metolazone, aspirin and clopidogrel), if two drugs act primarily on different organ systems because of the means of administration (e.g., anticholinergic effects of inhaled ipratropium bromide and oral biperiden), or if two drugs of the same class are commonly used in combination because of different pharmacokinetic properties (e.g., fentanyl patches and immediate release oxycodone for breakthrough pain).

For dose and dosing rate alerts, including adjustments for renal function, we made changes to multiple alert criteria and texts. Instead of calculating the eGFR using the Cockgroft-Gault formula, we used the Modification of Diet in Renal Disease study formula, since it does not require body weight, which is often not recorded in the EMR in bedridden patients. Moreover, if the body weight was not recorded, the CDSS could not perform dose checks for medications whose dosing was based on body weight. For these drugs, if supported by clinical practice, we transformed dose instructions for adults into actual doses irrespective of body weight (e.g., oral acetylcysteine, metoclopramide). Moreover, we replaced vague alerts by precise instructions for loading and maintenance doses according to specific stage of chronic kidney disease (e.g., metformin, ofloxacin) [Tables 2 and 3].

SPECIFIC RECOMMENDATION FOR FOLLOW-UP

For clinically significant drug-drug interaction alerts, we added simple instructions for dose adjustment and patient monitoring (e.g., instruction to reduce warfarin dose by 25–40% after introduction of amiodarone and close international normalized ratio follow-up; measuring tacrolimus plasma concen-

Table 1. Examples for modifications of drug-drug interaction alerts

Drug-drug interaction alerts			
	Text of original alert	**Action / Alert changes**	**Comment**
Prednisone and Tacrolimus	Enhanced immunosuppressants adverse effects may occur	Reduced to minor significance – no longer presented	Often used concomitantly
Propranolol and Salmeterol xinafoate	"May observe pharmacologic antagonism between the beta blocker and the beta agonist – bronchospasm may occur."	"Non-selective beta-blockers may reduce the efficacy of beta2-agonists (e.g. salbutamol) and cause bronchospasm. Consider using selective beta1-blocker"	The interaction is mainly relevant for non-selective beta-blockers
Warfarin sodium and Ceftriaxone sodium	Increased hypoprothrombinemic effect of anticoagulant with possible bleeding	Reduced to minor significance – no longer presented	Poor evidence, not listed in ACCP guidelines
Amlodipine and Simvastatin	No DDI alert	AMLODIPINE inhibits simvastatin's CYP3A4-mediated metabolism resulting in increased SIMVASTATIN levels and risk for statin myopathy. With concurrent therapy, the FDA recommends limiting SIMVASTATIN dose to 20 mg/day	Updating new FDA alert
Erythromycin/Clarithromycin/ Roxithromycin and Tacrolimus	No DDI alert	"Many macrolides (e.g., erythromycin, clarithromycin, roxithromycin) inhibit CYP3A4 and may result in elevated levels of tacrolimus and resultant toxicity, including QTc prolongation and Torsades de Pointes ventricular tachycardia. Consider monitoring tacrolimus concentrations and ECG recordings"	According to latest evidence

DDI = drug-drug interaction, ACCP = American College of Chest Physicians

Table 2. Examples for modifications of drug dosing alerts

Drug dosing alerts			
	Text of original alert	**Action/Alert changes**	**Comment**
Acetylcysteine per os	Please update patient weight. Dosage check was not performed due to missing patient weight	Dose recommendations changed from weight-based doses to fixed doses	For indications other than paracetamol overdose, fixed doses are commonly used
Clopidogrel bisulfate (tablet)	The recommended maximal single dose should not exceed 75 mg	The recommended maximal single dose should not exceed 600 mg	Recommended loading doses are 300–600 mg given once
Tramadol HCL (drops)	Rx: 100 mg PO x 1. Frequency is below the recommended frequency of 2 day	Minimal frequency was changed from 2 to 1/day	More flexibility to adjust dosing to pain pattern
Phenytoin sodium (capsule)	Rx: 200 mg PO x 2. Frequency is below the recommended frequency of 3 per day	Minimal daily frequency reduced to 1/day	Daily dose is often given as single dose
Piperacillin sodium/ Tazobactam sodium	The recommended maximal single dose should not exceed 4 g	Change of maximal single dose to 4.5 g	New dosing recommendation refers to the vials available in Israel
Potassium chloride (tab. SR 8 HR)	Rx: 600 mg PO x 1. Frequency is below the recommended frequency of 2 per day	Minimal daily frequency changed to 1/day	To allow more flexibility depending on patient's serum potassium and eGFR

trations and performing an electrocardiogram after adding azithromycin; monitoring potassium blood levels after adding prednisone to amphotericin B).

CHANGES OF ALERT WORDING AND TYPOGRAPHY

To enhance comprehensibility we rephrased alerts that were unclear (e.g., for the interaction between iron tablets with ofloxacin, we replaced the original alert *["Anti-infective action of quinolones may be decreased"*] with the following text: "*Concomitant administration of oral quinolones with oral iron, aluminium, or magnesium preparations may reduce quinolone absorption by up to 50%. Separate administration by at least 6 hours*"). For patients with decreased renal function, we presented the latest eGFR together with dose instructions appropriate for that particular level of renal function. Additionally, we improved the graphic presentation of alerts for greater clarity and uniformity (e.g., color coding for different alert types, dosing instructions presented in capital letters, dose adjustments for decreased renal functions presented in blue).

DISCUSSION

This manuscript describes the implementation and customization of a CDSS for medication prescription in a large tertiary-care hospital, and the attending challenges and opportunities. While prescription errors related to illegible handwriting and misspelled drug names are effectively prevented by CPOE systems, such systems do not alert the physician to other potential prescription errors, such as drug-drug interactions, dosing errors, or duplicate therapy. "Intelligent" computerized decision support systems are increasingly used to address these deficiencies. Although the definition of a prescription error will depend on the surveillance method and adjudicating body, thus generating large heterogeneity among different studies, CPOE systems with CDSS have been estimated to reduce prescription errors by 48%, with an attending reduction of adverse drug effects [11]. However, the introduction of CDSS has also been met with opposition.

CDSS alerts cause interruption in the workflow, forcing the user to acknowledge the alert before proceeding with the prescribing, and are thus often considered a nuisance [12]. Most importantly, the frequent presentation of alerts quickly leads to "alert fatigue," where the prescriber is desensitized by a flood of alerts, often with little clinical relevance, and then ignores cru-

Table 3. Examples for modifications of dose adjustments for renal function

Adjustment for decreased renal function alerts			
	Text of original alert	**Action/Alert changes**	**Comment**
Ofloxacin (tablet)	eGFR = 31 ml/min/1.73 m². Adjustment for CrCl (general guidance): CrCl = 20–50. Loading: administer one single dose adequate for normal renal function. Maintenance: administer single dose once a day	For CrCl = 20–50 Administer usual loading dose (200–400 mg), then 50% of maintenance dose, e.g., 200–400 mg x 1/day	Different doses depending on the indication
Vancomycin HCL	eGFR = 20 ml/min/1.73 m². **Remark:** Dose per 24 hours: 310 mg	**Remark:** Recommended loading dose is 15 mg/kg. For CrCl 10–30 ml/min, estimated maintenance dose 150–500 mg/24 hours. Maintenance dose and frequency depend on indication, target trough plasma concentrations, and renal function. Monitor trough vancomycin plasma concentrations and adjust accordingly	According to updated recommendations for dosing and therapeutic drug monitoring
Metformin HCL	eGFR = 39 ml/min/1.73 m². CCT general guidance: use is contraindicated	30<eGFR<45: Use with caution. Metformin accumulates in patients with renal failure	According to current guidelines/ recommendations
Enoxaparin sodium	eGFR = 20 ml/min/1.73 m². Adjustment for CrCl (general guidance): Reduced drug clearance and increased bleeding risk	For CrCl = 11–30: "Reduce dose by 50% of regular maintenance dose, e.g., 1 mg/kg x 1/day (therapeutic dose) or 20 mg x 1/day (preventive dose). If prolonged therapy is planned at therapeutic doses, consider anti-Xa monitoring, or therapy with unfractionated heparin instead"	Precise dose instructions according to best available evidence

cial alerts with potentially critical consequences – the "cry wolf" effect [21]. Thus, in clinical practice, alerts are often overridden without even being read, reducing the CDSS effectiveness. In most surveys, 49–96% of alerts are overridden, many presumably without a thorough consideration of the pharmacological issues at hand. Therefore, the reduction of number of alerts and customization to the specific needs of the department is considered essential for improving the CDSS's signal-to-noise ratio and for its effectiveness in clinical practice.

There are no consensus criteria for silencing alerts [21,22]. Indeed, any modification of alert systems raises medico-legal concerns, in particular fear of litigation in cases where warnings were removed that could have prevented a prescribing error resulting in patient harm [23]. However, all-inclusive CDSS systems, in fact a manifestation of "defensive medicine," quickly lose effectiveness and therefore their primary purpose. Thus, alert silencing and CDSS customization are crucial and ongoing requirements during CDSS implementation and maintenance [23].

We prioritized alerts according to their potential clinical significance and prevalence, the presumed experience of the physician in a given department with a given drug combination, and physicians' comments and feedback. Thus, many drug-drug interactions have little scientific documentation (e.g., only case report level of evidence) or only small potential clinical impact, resulting in a change of prescription in a small minority of cases (2%–12%) [24]. We presumed that physicians were familiar with interactions between drug combinations that were common in a given department (e.g., aspirin and clopidogrel) and that the corresponding alert was therefore redundant. On the other hand, we expanded alerts relating to dosing errors, especially in patients with reduced renal function, because these alerts usually represent true prescribing errors that are more likely to result in adverse drug events [7]. Silencing criteria depended on the department specialty and specific requests of individual departments. For example, duplicate therapy alerts for diuretic drugs of different classes and drug-drug interaction alerts with aspirin and low molecular heparins were very common in internal medicine departments and were therefore silenced there but remained active in other departments.

In our preliminary analysis, the mean number of prescriptions per patient (11.2 ± 0.5) and the fraction of prescriptions that triggered CDSS alerts (30.1%) were comparable to findings in previous studies [24]. However, in view of the high patient turnover in our internal medicine departments, the absolute number of alerts was high – a staggering 1400 alerts per department each month. Although most of these alerts may have been "soft alerts" that were unlikely to result in patient harm, there was a considerable number of "hard alerts" with greater potential for patient harm, such as approximately 330 monthly alerts for a lack of dose adjustment for decreased renal function, and 46 major drug-drug interaction alerts. Thus, in each department, more than 12 daily prescription errors with higher likelihood for patient harm could be potentially prevented by the CDSS.

The high number of alerts in our preliminary analysis attests to the continued need for alert silencing. In the current study we did not assess alert fatigue among physicians, or the effectiveness of alerts in changing the prescription where necessary. However, for physicians with a high prescription rate, such as

residents in internal medicine departments, it is likely that an alert rate of > 30% will quickly lead to alert fatigue and reduced effectiveness of the CDSS. Thus, there is an obvious need for continuing alert reduction, at the stage of both CDSS implementation and maintenance. Moreover, changes in the institution's drug formulary, changes in therapeutic guidelines, and new information on drug safety will have to be continuously updated. Thus, CDSS implementation requires a multidisciplinary team of clinical pharmacologists, pharmacists, information technology experts, and representatives of the specific hospital departments to continuously customize and maintain the system and thus assure its effectiveness [21,25].

Other than kidney disease, our CDSS does not address drug-disease interactions or omission errors, situations in which patients during their hospitalization are inadvertently not prescribed the medications they should receive according to their medical diagnosis or their chronic medication list. More sophisticated CDSS that interface with ambulatory medication lists provided by the health maintenance organizations and with the patient's medical problem list will be required for reducing these types of medication error.

In conclusion, to ensure its effectiveness, the implementation of a commercial CDSS in a large hospital requires system customization guided by the specific needs of particular departments, at both the initial and the maintenance stage. This task is best achieved by a multidisciplinary team in collaboration with the end-user (the representatives of the prescribing physicians). Future research establishing guidelines for drug silencing and exploring features that improve CDSS effectiveness will be of interest.

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"The best portion of a good man's life is his little, nameless, unremembered acts of kindness and of love"

William Wordsworth (1770-1850), major English Romantic poet