Drug Safety Alerting in Computerized Physician Order Entry

Unraveling and Counteracting Alert Fatigue

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Unraveling and Counteracting Alert Fatigue

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Ontrafelen en tegengaan van signaalmoeheid

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Chapter 1

General introduction

INTRODUCTION

In modern healthcare, prescribing drugs is one of the forms of medical treatment most frequently used [1,2]. The medication process consists of different phases: drug prescribing, dispensing and administration, and errors may occur in every phase of this process [2]. Prescribing drugs electronically is considered an important measure to reduce errors in the first phase of the medication process. A system enabling clinicians to enter medical orders electronically is called a computerized physician order entry (CPOE) system [3]. CPOE systems are frequently accompanied by a decision support system. Decision support systems attempt to improve decisions taken by clinicians through advice, alerts and reminders [3].

Implementation of CPOE with integrated decision support has been shown to result in error reduction because of better legibility and decision support. A study in the United States showed an 81% reduction in non-missed dose medication errors and an 86% reduction in non-intercepted serious medication errors when a CPOE system was utilized [4]. These reductions were only achieved after 4.5 years of error measurements, error analysis and adjustments of the decision support system.

In the Netherlands, the introduction of CPOE was preceded by order entry within pharmacy systems. Dutch community pharmacies have a long history of drug safety alerting and the Netherlands has a single national drug database (G-standard) containing information on doses and drug-drug interactions among others, to enable drug safety alerting [5]. This national drug database is used as a knowledge base for all pharmacy systems and CPOEs within and outside hospitals.

Many Dutch hospital pharmacies used to enter handwritten orders in electronic systems with drug safety alerting. However, order entry by hospital pharmacies often took place after the drug had been administered, so alerts were generated too late. Furthermore, order entry by hospital pharmacies did not prevent interpretation problems of illegible handwritten orders and the corresponding transcription errors. In Dutch hospitals implementation of CPOE for medication started in the nineties of the last century [6,7].

In the Erasmus University Medical Center, CPOE with integrated clinical decision support was implemented between 2001 and 2006. Since implementation physicians have been entering medication orders electronically and they have been confronted with drug safety alerts for overdoses, duplicate orders and drug-drug interactions that pop-up during the order entry process.

The first ideas for the research described in this thesis arose in 2003. As a project leader of the CPOE in Erasmus MC, I received several user complaints about the clinical decision support incorporated in the system. Physicians complained about the CPOE generating too many alerts that were not useful, and they admitted to frequently overriding them without reading them, i.e., to confirming the order despite the alert.

These disclosures alarmed me. An overload of drug safety alerts could result in an increased risk of alert fatigue, important alerts being ignored along with unimportant ones and in a false sense of safety with an increased risk of adverse events. The intended error reduction and safety improvement of CPOE implementation would be impaired. At the same time these user complaints raised my interest and many questions came to mind. What was the magnitude of the problem? Why did physicians override drug safety alerts? Was overriding dependent on the CPOE, the specialty of the physician, or alert type? Did alert fatigue really exist? Was it preventable?

The process of alert generation and handling can be summarized as shown in Figure 1. The knowledge base and the CPOE determine alert generation; physicians have to handle these alerts, and this handling has its effects on the patient for whom orders are entered. All parts of this process should be studied to answer the abovementioned questions.

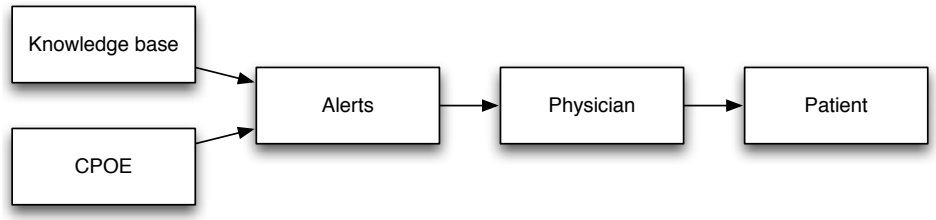

Figure 1 Process of alert generation and handling

SCOPE AND AIM OF THE THESIS

The studies combined in this thesis aim to increase the knowledge and understanding of drug safety alert handling in computerized physician order entry systems. The first part of the thesis aims to gain an insight into alert generation and overriding in order to unravel the problem of alert fatigue. The second part describes several attempts to counteract alert fatigue by decreasing the burden of excessive numbers of alerts.

The following questions are addressed in this study:

1. How often and in what kind of situations are safety alerts overridden?
2. Why do physicians override them?
3. What kind of errors are made in alert handling?
4. What is the quality of drug safety alerting in Dutch CPOE systems?
5. Can the burden of excessive numbers of drug-drug interaction alerts be decreased safely by
    a. Turning off frequently overridden alerts?
    b. Adding levels of seriousness to the alert text?
    c. Directing alerts to other people in the workflow?
    d. Increasing specificity?

These questions will be addressed in the studies presented in chapters 2 and 3.

Chapter 2 describes studies gaining an insight in alert generation and overriding. Firstly, chapter 2.1 gives an overview of the available literature on overriding drug safety alerts in CPOE. We applied Reason's model of accident causation to drug safety alerting to understand overriding and its effects.

Quantification of alert generation and handling in daily practice is the subject of chapter 2.2. It describes the number and types of alerts generated and overridden in a large Dutch University Medical Center. The research techniques for this study were disguised observation of residents entering medication orders during their normal work, and retrospective analysis of overridden alerts.

Chapter 2.3 addresses the question of why physicians override or annul drug safety alerts, which errors are made and which cognitive processes play a role. This was a laboratory study with patient cases and different types of known and unknown drug safety alerts and with residents from internal medicine and surgery who did not know the real objective of the study. We observed the physicians handling the drug safety alerts and directly afterwards interviewed them about reasons and causes for their actions.

Chapter 2.4 does not focus on user actions but on the quality of drug safety alerting of the prescribing systems. Do CPOEs generate alerts when required and do they prevent unnecessary alert generation? We developed a test based on the Dutch national drug database and tested the hospital CPOEs at vendors' offices. We attempted to estimate effects on patient safety by discussing the results with hospital pharmacists.

The second part of this thesis, presented in chapter 3, focused on measures to decrease the burden of excessive drug-drug interaction alerts. It started with an attempt to turn off drug-drug interaction alerts in the hospital context (chapter 3.1). We asked residents and specialists from internal medicine, cardiology and surgery, and hospital pharmacists, whether 24 frequently overridden alerts could be turned off hospital-wide safely and the reasons for their decisions.

The second study, described in chapter 3.2, aimed to facilitate alert interpretation and handling by changing the information content of the alert. We added the level of seriousness to the alert text and studied numbers of overridden alerts. Furthermore, we asked physicians how they valued this information.

The topic of the next three chapters was patient risk due to overriding. In chapter 3.3 we report on drug administration errors due to overriding time-dependent drug-drug interaction alerts and how the effect of feedback and the possibility of directing alerts to other people in the workflow (nurses) were studied.

QT prolongation overrides were the object of our study in chapters 3.4 and 3.5. First we studied whether an electrocardiogram was recorded following a QT override and how often patients were at risk of developing Torsades de Pointes. In chapter 3.5 we report on whether an adjustment in the Dutch national drug database, aimed at improving specificity resulted in the effects intended.

In chapter 4, we put all findings together to discuss whether the model proposed in chapter 2.1 is useful and how alert fatigue should be defined and counteracted. Furthermore, we give recommendations for future research. This thesis ends with a summary and conclusions in chapter 5.

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Chapter 2

Insight in generation and handling of drug safety alerts

Chapter 2.1

Overriding of drug safety alerts in computerized physician order entry

Heleen van der Sijs, Jos Aarts, Arnold Vulto, Marc Berg

ABSTRACT

Many computerized physician order entry (CPOE) systems have integrated drug safety alerts. The authors reviewed the literature on physician response to drug safety alerts and interpreted the results using Reason's framework of accident causation. In total, 17 papers met the inclusion criteria. Drug safety alerts are overridden by clinicians in 49 to 96% of cases. Alert overriding may often be justified and adverse drug events due to overridden alerts are not always preventable. A distinction between appropriate and useful alerts should be made. The alerting system may contain error-producing conditions like low specificity, low sensitivity, unclear information content, unnecessary workflow disruptions, and unsafe and inefficient handling. These may result in active failures of the physician, like ignoring alerts, misinterpretation, and incorrect handling. Efforts to improve patient safety by increasing correct handling of drug safety alerts should focus on the error-producing conditions in software and organization. Studies on cognitive processes playing a role in overriding drug safety alerts are lacking.

INTRODUCTION

Computerized physician order entry (CPOE) systems frequently include integrated decision support components, which can reduce errors and improve patient safety [1-6]. Studies documenting positive effects of decision support on patient outcomes, including fewer duplicate orders, fewer overdoses, fewer allergic reactions, and reduced drug interactions, have prompted calls for additional safety-related, patient-specific advice [1,3,5]. Yet, the burden of reminders and alerts must not be too high [1,2,6-8], or alert fatigue may cause clinicians to override both important and unimportant alerts [2,9], in a manner that compromises the desired safety effect of integrating decision support into CPOE.

This review attempts to provide insight into physicians' handling of safety alerts by asking the following questions: How often and in what situations are safety alerts overridden? Why do physicians override them? What effects ensue? What understanding of alert overrides can lead to improved alerting systems? The authors employ Reason´s model of accident causation [10] to understand overriding and its effects and to suggest new directions to improve alerting.

METHODS

The MEDLINE and EMBASE databases from January 1980 to December 2004 were searched for English language publications with the following MeSH headings and text words: computerized physician (medication) order entry, CPOE, electronic prescribing, computerized prescribing, medical record systems computerized and alert*, remind*, prompt*, order check, critic*, critiq*, decision support systems clinical, reminder systems, drug therapy computer assisted and overrid*, medical error, adverse drug events and attitude. The authors also checked literature references of three recent systematic reviews and one synthesis of review paper [1,3,5,11].

The authors selected publications discussing overriding of unsolicited drug safety alerts that appear during the prescription process because automatic provision of alerts has been proven to be a critical feature for changing clinician behavior [12]. The term computerized physician order entry is used because interpretation and handling of drug safety alerts requires medical expertise. Full articles were included, but also proceedings when pertinent. The references of these publications were checked also. The refined selection was used for the first part of this review. To learn how alerting could be improved, the authors examined all publications from the search for characteristics of unsolicited safety alerts as well as measures to minimize error-producing conditions.

RESULTS

Seventeen publications on overriding safety alerts in CPOE were identified [2,13-28] (Table 1). Quantitative information on overriding was present in nine publications [13-21]. This small yield does not pose a problem, because the review focuses mainly on the conceptual analysis of

Table 1 Publications on overriding drug safety alerts during the order entry process

Investigator Year of publication	Type of publication	Type of clinic	Type of alerts	Type of research	Quantitative or Qualitative
Nightingale, 2000[13]	Full article	Teaching hospital Birmingham, USA	Drugs	Order analysis, questionnaire survey	Quantitative Qualitative
Abookire, 2000[14]	Proceedings	Teaching hospital Boston, USA	Drugs	Order analysis	Quantitative
Peterson, 2001[15]	Abstract	Teaching hospital Boston, USA	Drugs	Order analysis	Quantitative
Payne, 2002[16]	Proceedings	Teaching hospital Seattle, USA	Drugs	Order analysis	Quantitative
Oppenheim, 2002[17]	Proceedings	Teaching hospital New York, USA	Drugs	Order analysis	Quantitative
Kalmeijer, 2003[18]	Full article	Teaching hospital Amsterdam, the Netherlands	Drugs	Unknown (topic of article is implementation)	Quantitative
Weingart, 2003[19]	Full article	Primary care, Boston, USA	Drugs	Order analysis	Quantitative
Hsieh, 2004[20]	Full article	Teaching hospital Boston, USA	Drugs	Order analysis	Quantitative
Taylor, 2004[21]	Proceedings	Primary care, Montreal, Canada	Drugs	Order analysis	Quantitative
Magnus, 2002[22]	Full article	General practitioners, UK	Drugs	Questionnaire survey	Qualitative
Ashworth, 2002[23]	Commentary on Magnus				Qualitative
Glassman, 2002[2]	Full article	Ambulatory care and community clinics, USA	Drugs	Questionnaire survey	Qualitative
Overhage, 1997[24]	Full article	Teaching hospital Indianapolis, USA	Corollary orders (drug-lab)	Randomized controlled trial	Quantitative
Krall, 2001[25]	Proceedings	Primary Care, Portland, USA	Best Practice, Health Maintenance	Questionnaire survey	Qualitative
Krall, 2002[26]	Proceedings	Primary Care, Portland, USA	Best Practice, Health Maintenance	Focus groups	Qualitative
Ahearn, 2003[27]	Full article	General practitioners, Australia	Drugs	Focus groups	Qualitative
Feldstein, 2004[28]	Full article	Primary care, Portland, USA	Drugs and Health Maintenance	In-depth interviews	Qualitative

the determinants of overriding. For the second part of this article, we selected from 193 papers of the first search those that described characteristics of safety alerts.

How often and in what kind of situations are safety alerts overridden?

Papers discussing percentages of overridden alerts of different types are summarized in Table 2 [13-21]. Except for serious alerts for overdose, which are overridden in one fourth of all alerts, safety alerts are overridden in 49 to 96% of cases. Taylor and Tamblyn [21] show lower override rates for interactions (35%) and contraindications (43%), but this seems to be caused by an extra toxicity category also including interactions and contraindications. Bates et al. [11] propose a maximum override rate of 40%, but do not offer an explanation for this figure.

Low-level alerts appear to be overridden more often than high-level alerts (serious alerts), but this could not completely confirmed in a study with three levels of alerts [13,14,19]. Moreover, alert levels cannot be compared between studies because standardization of alert levels is absent. None of these quantitative studies discusses the relationship between different levels of alerts and override rates.

One study showed a rise in override rates from about 50 to 75% during a five-year period, indicating a declining compliance to safety alerts [14]. A relationship between relative amount of alerts and percentages overridden cannot be observed, but this may be due to the small number of studies [13,16-19,21]. High override rates were observed in drug renewals, in drug interactions with topical drugs and in poorly defined drug allergies [14,16,19,20].

Factors that play a role in overriding

Three studies elucidated factors playing a role in overriding alerts by physicians in outpatient care [21-23,28]. The most important reason for overriding was alert fatigue caused by poor signal-to-noise ratio because the alert was not serious, was irrelevant, or was shown repeatedly [2,21,22,28]. Alert fatigue is as yet not thoroughly studied but is described as the mental state that is the result of too many alerts consuming time and mental energy, which can cause important alerts to be ignored along with clinically unimportant ones [9]. Other reasons include the importance of the treatment not allowing a drug change, physicians' faith in their own knowledge or other information sources obtained, incorrect information, patients' resistance to drug change or lack of time [21,22]. It was also mentioned that alerts were too long and difficult to interpret and that clinical consequences were not clear [23,28]. Twenty-two percent of general practitioners admitted drug interaction overriding without checking [22]. In a study on corollary orders, reasons not to accept reminders included inappropriate orders, disagreement with the guideline, and lack of time [24]. Lack of understanding about importance of the warning, technological problems and unnecessary workflow interruptions also thwart correct and effective handling of safety alerts [2,26,27].

Two studies reviewed appropriateness of the alerts and revealed that 36.5 and 39% of the alerts were false positive [17,19]. Reviewers agreed with clinicians´ decisions in 95.6% of cases

where physicians overrode a valid alert [19]. Oppenheim et al. [17] found that 48% of the true positive alerts were overridden.

Table 2 Override rates of drug safety alerts

Investigator, Year of publication	Duration of measurement	Number of orders	% alerts/ number of orders	% override rate	Kind of alert(s)
Nightingale, 2000[13]	11 months	87,789	20	90	Contraindication, drug-drug interaction, overdose
				73	High-level contraindication
				85	Low-level contraindication
				85	High-level interaction
				93	Low-level interaction
				27	High-level overdose
				53	Low-level overdose
Abookire, 2000[14]	5 years	*		49-73	Definite allergy-drug interaction
				54-80	Possible allergy-drug interaction
Peterson, 2001[15]	6 months	*		57	7 life-threatening drug-drug interactions
Payne, 2002[16]	4 weeks	42,641	11	78	Drug-drug interaction, drug-allergy interaction
				88	Critical drug interaction
				69	Drug-allergy interaction
Oppenheim, 2002[17]	3 months	4,596	11	68	Incorrect dose in renal patients
				48	True positive incorrect dose in renal patients
Kalmeijer, 2003[18]	1 year	150,358	36	90	Drug-drug interaction, overdose, duplicate orders
Weingart, 2003[19]	3 months	24,034	14	94	Drug-drug interaction, drug-allergy interaction
				91	Drug-allergy interaction
				89	High-level interaction
				96	Medium-level interaction
				85	Low-level interaction
Hsieh, 2004[20]	3 months	*		80	Drug-allergy interaction
Taylor, 2004[21]	3 months	6260	30	55	Contraindications, allergy, intolerance, incorrect dose, duplicate orders, drug-drug interaction, toxicity
				43	Contraindication
				92	Allergy and intolerance
				90	Incorrect dose
				86	Duplicate orders
				35	Drug-drug interaction
				84	Toxicity

* not documented

Effect of overridden alerts

The direct effect of overridden alerts on safety is mentioned in three publications. Adverse events were observed in 2.3, 2.5 and 6% of the overridden alerts, respectively, in studies with override rates of 57, 90, and 80% [15,19,20]. Adverse events were preventable in 0.8% and none of the overrides, respectively [19,20].

A high override rate can also indirectly impair patient safety. Too many alerts with low credibility may cause physicians to override important alerts along with unimportant ones. A high override rate might also result in the hospital decision to turn off a whole group of alerts, including relevant alerts, or in decreased user acceptance and distrust in both the alerting system and CPOE [16,22,27,29]. Monitoring of overriding is said to be necessary to keep the override rate within acceptable limits and to ensure user trust and responsiveness to alerts [14].

UNDERSTANDING THE EFFECT OF OVERRIDING DRUG SAFETY ALERTS ON PATIENT SAFETY

Integrated decision support should prevent patients from receiving the wrong drug or the wrong dose when prescription errors are made. However, not all errors are caught because alerts are turned off, are not read, are misinterpreted, or are wrongly overridden. In Figure 1, the process of order entry, interpretation, and handling of drug safety alerts and the emergence of medication errors are presented schematically.

Figure 1 may help explain why overriding does not always result in a medication error. There can be good reasons for overriding (justified overriding), for example, when the benefits of the drug (combination) outweigh the disadvantages, and potential adverse effects can be monitored [19]. Conversely, a cancellation or change of a drug order due to a drug safety alert can itself result in a medication error. Overriding a safety alert is often seen as a problem in itself, a system violation, but it should be emphasized that only *unjustified* overriding (ignoring alerts, misinterpretation, wrong selection) poses a problem.

Justified overriding may be patient related or can occur when an alert is based on erroneous patient information. Patient-related reasons include, for example, clinically insignificant alerts, a limited treatment course, patient tolerance of the medication or dose in the past, discussion of potential adverse events with the patient or monitoring thereof, absence of a good alternative, and the benefits of the drug outweighing the disadvantages [19]. Examples of erroneous patient information, justifying overriding, include inaccurate allergy information or medication lists that are out of date [19,30]. Appropriate alerts can be defined as true positive alerts, alerts that are correct and current for the patient at hand. It does not imply that appropriate alerts are always perceived as useful.

The authors suggest that problems of safety alert overriding can be explained with the help of Reason's model of accident causation. This model is applicable to complex sociotechnical

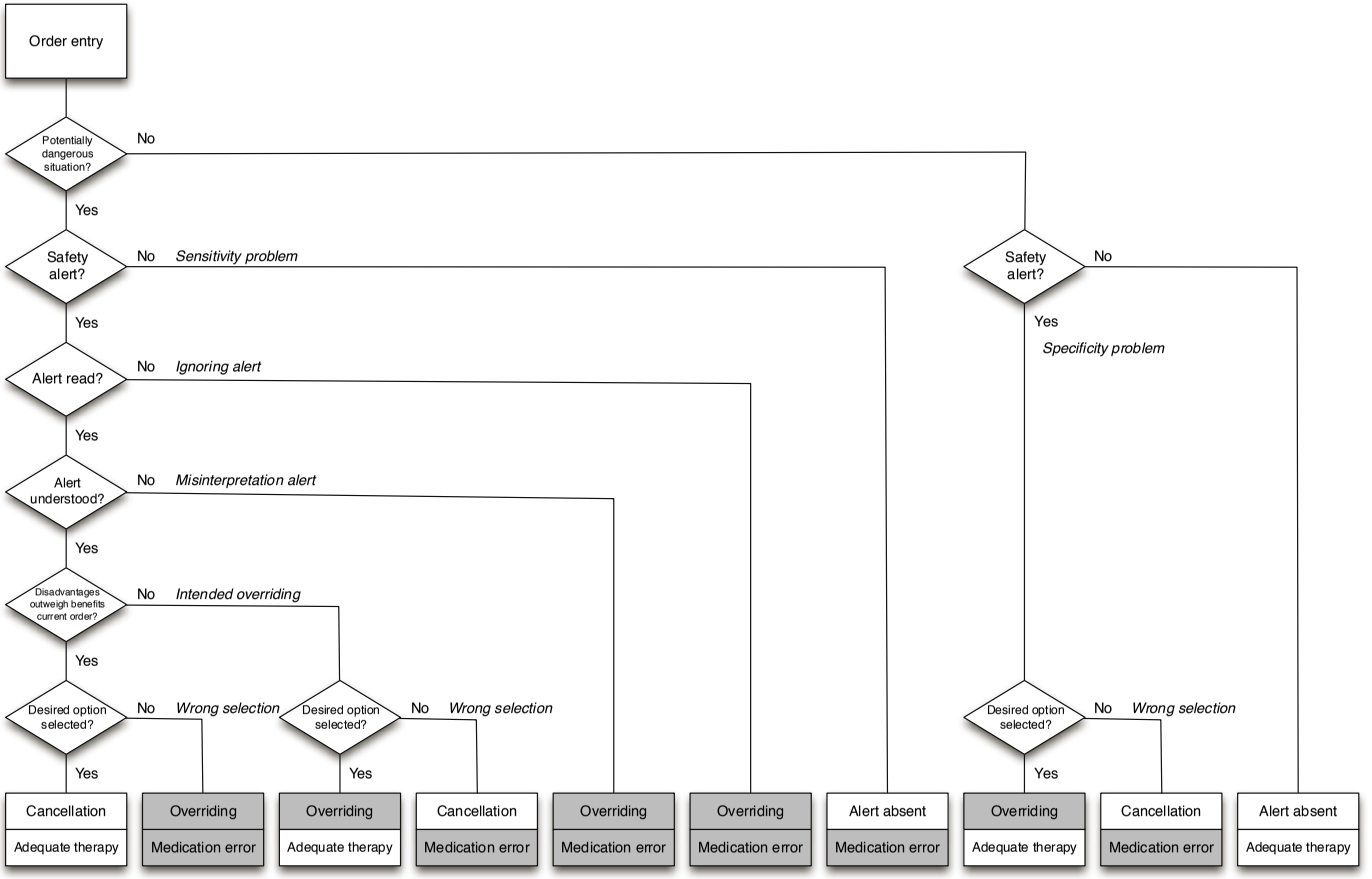

Figure 1 Process of order entry and handling of safety alerts in CPOE

systems that require coordination of a large number of human and technologic elements and focuses on person, team, task, workplace and organization [10,31]. Alerting systems in CPOE are an example of such a complex sociotechnical system.

Reason distinguishes between active failures, error-producing conditions and latent conditions [10,31-33]. Active failures are errors (slips, lapses and mistakes) and violations of an individual having an immediate adverse effect. Error-producing conditions are factors that affect performance of individuals, thus provoking active failures. These factors can originate in the environment, team of care providers, individual or task at hand. Latent conditions are defensive gaps, weaknesses and absences that are unwittingly created as the result of earlier decisions made by system designers, builders, regulators, and managers. Latent conditions can originate from organizational processes or management decisions. Reason's model shows that accidents result from a concatenation of several contributing factors at different levels: active failures, error-producing conditions and latent conditions; individual and organizational factors. Simultaneous alignment of gaps or absences within diverse and redundant defenses results in accidents [10,31,32,34].

Figure 2 shows how active failures leading to medication errors are the result of error-producing conditions in alerting system and physician, and latent conditions in the organization [35]. It shows how suboptimal decision support can reduce physicians´ motivation, thus provoking active failures in alert handling.

Studies that linked overriding to adverse events showed that overriding did not result in adverse drug events in more than 97% of cases [15,19,20]. Figure 1 shows that overrides might result in adequate therapy as well as medication errors. A medication error is any error in the

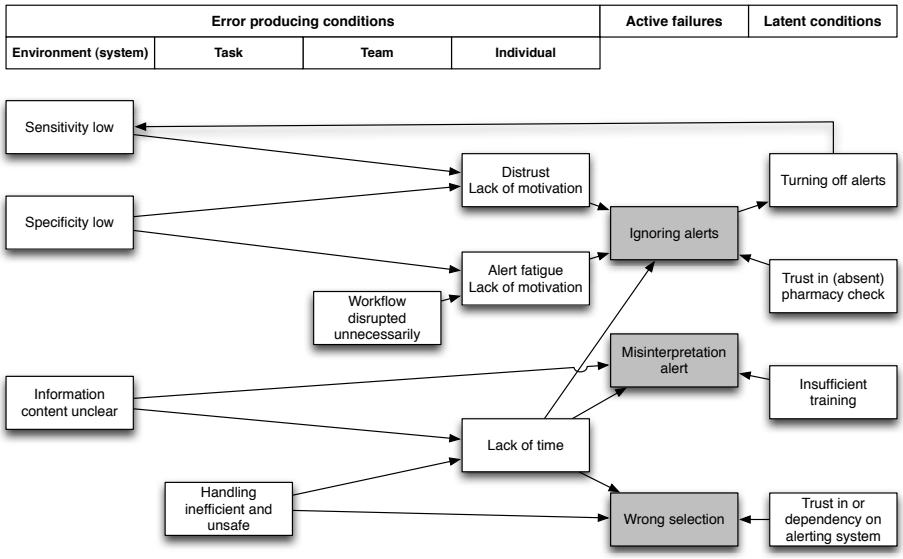

Figure 2 Reason´s model applied to drug safety alerts in CPOE

process of prescribing, dispensing or administering a drug, whether or not there are adverse consequences [36]. Unjustified overriding of a drug safety alert (medication error) does not necessarily have adverse consequences. Overriding may, for example, result in suboptimal treatment or may be annulled by a dispensing or administration error. Conversely, adverse drug events can also result from justified overriding [20], or intrinsic drug toxicity [37]. The relationship between overridden alerts and adverse drug events, presented in Figure 3 shows that appropriate alerts can be overridden and that overriding does not necessarily result in adverse drug events. It shows also that justified overriding (adequate therapy) cannot always prevent adverse events.

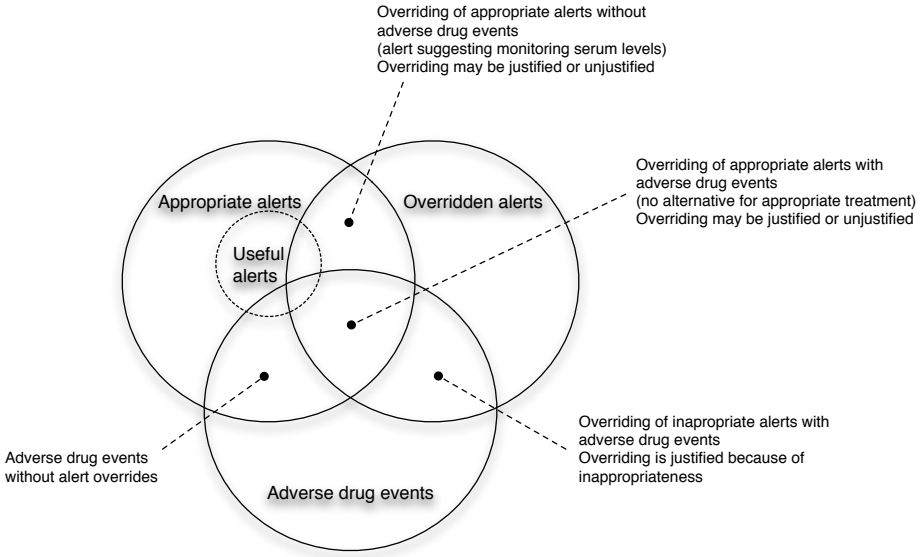

Figure 3 Relationship between appropriate alerts, overridden alerts and adverse drug events
Appropriate alerts = true positive alerts
Overridden alerts = alerts that did not result in cancellation or change of order
Adverse drug event = patient morbidity due to medication errors and/or intrinsic drug toxicity

Two studies describe how expert panels review patient charts and score adverse events [15,19]. For justification of overriding, it is easier to score override decisions, which gives more information about reasons [20,38]. Requiring entry of reasons for overriding is more feasible for daily practice, triggers physicians to rethink the potential unsafe situation, gives pharmacists and other caregivers insight in the considerations, and can help adjust the knowledge database.

Alerting systems may contain several error-producing conditions increasing the risk of a medication error.

IMPROVING ALERTING

A safe alerting system has high specificity and sensitivity, presents clear information, does not unnecessarily disrupt workflow, and facilitates safe and efficient handling. Several qualitative studies of safety alerts in CPOE present requirements and suggestions for alerting systems [2,7,9,12,19,20,22,26,28,39-41]. Alert factors applicable to unsolicited drug safety alerts are presented in Table 3, grouped by the five items for a safe alerting system and classified as necessary for appropriate alerts or useful for safe and efficient interpretation and handling.

Improvement of alerting systems should focus on prevention of active failures and individual error-producing conditions (distrust, alert fatigue, lack of motivation, and lack of time), by reducing or removing error-producing conditions of system, task and team, and latent conditions. Error-producing conditions have a more direct effect on active failures and can be influenced more easily than latent conditions.

If physicians ignore alerts, they often do so because alerts are inappropriate [2,22]. The authors suggest that the first step to reduce the frequency of ignoring alerts should be reducing the number of inappropriate (false positive) alerts and to direct certain alerts to other care providers, thus preventing unnecessary disruptions in physicians' workflow. After increasing appropriateness, sensitivity, usefulness, and usability should be improved. Improving sensitivity may result in a unacceptable time burden for the physician if interpretation and handling are inefficient. If sensitivity is low and handling efficient, sensitivity should first be increased. When error-producing conditions are reduced or removed, latent conditions should be addressed.

Increasing specificity

To increase the percentage of appropriate alerts (specificity), irrelevant and nonurgent alerts should not be shown and alerts should be patient tailored. Alerts that should not be shown are interactions between systemic and topical drugs, alerts of drug allergy in case of medication intolerance, and alerts without urgent or possible action [14,16].

To tailor alerts to the patient at hand, age, gender and body weight, allergies, mitigating circumstances and drug serum levels should be taken into account. The Dutch national drug database, updated monthly, recently added dose ranges dependent on age and body weight and included a gender indication on gender-specific drugs to improve specificity. If alerts are only important if specific serum levels are high, alerts should be suppressed if the level is low [9]. Mitigating allergy alerting should be possible in case of medication intolerance [14,26]. If a potential interaction did not result in problems in a particular patient, physicians should have the possibility to prevent the interaction alert in dose adjustment in that patient. Entering (coded) overriding decisions should prevent future alert generation [20,38].

A pharmacist or nurse can deal with low specificity alerts that can be checked once daily, for example, rising laboratory values like creatinine, possible switch from intravenous to oral medication, or polypharmacy [41]. They can present these alerts with additional information

Table 3 Factors for appropriate and useful alerts

	Issue	Requirements/suggestions	Appropriate	Useful
Specificity	Specificity[2,9,39]	alerts should be clinically important for the patient	X	X
	Relevance[19,39]	alerts should not be of minor importance	X	X
	Urgency[26]	action should follow the alert (is required and is possible)	X	X
	Accuracy[26]	alerts should be presented at the patient level: right patient, gender, age should be used, as well as known allergies and serum levels	X	X
	Exceptions, repetition[7,14,19,20,26]	entering exceptions or mitigating circumstances should be easy to influence the number and accuracy of future alerts positively	X	X
Information content	Unambiguity[12,28]	Information must be clear and unambiguous		X
	Justification[39]	justification of the recommendation should be shown, no black box-warnings		X
	Conciseness[26,28,39]	Amount of information should be limited, initial triage should be possible at a glance		X
	Accessibility[26,28,39]	more information should be easily accessible (in the program itself and/or in other knowledge sources)		X
	Seriousness[14,19,27]	the seriousness of the alerts should be clear		X
	Alternative[12,19,26]	alternative action should be presented		X
Sensitivity	Sensitivity[2,7]	alerts must be generated in all dangerous cases		X
Workflow	Workflow[26,40]	alerts should be directed to the right person; low specificity alerts or administration alerts can be presented to nurses or pharmacy	(x)	X
	Knowledge specific[26]	specialist should receive less alerts than residents		X
	Specialty specific[26]	specialist should receive no alerts on his own specialty		X
	Repetition[26]	annoying repetition should be prevented, turning off the alert (for a certain period) should be possible if user performs well		X
Safe and efficient handling	Seriousness[22]	overriding fatal alerts should not be easy (high threshold)		X
	Reasoning[12,19,20]	reasons for any noncompliance should be requested		X
	Non-inquisitive alerts[11,12,39]	system should not ask for more data entry		X
	Action[11,12]	promoting of action, rather than stopping intended action		X
	Speed[11,26]	system must have speed		X
	Screen design[26]	size and place of buttons should be logical, ensuring speed and error reduction		X
	Work to be done[11,26,28]	minimizing scrolling, keystrokes, typing, mouse clicks, steps to accomplish a task, screen or window changes, switching between keyboard and mouse		X

and a proposal to the physician [4]. Directing alerts to other people in the workflow can also be used temporarily to test and improve new alerting features [41]. Alerts about administration can be directed to nurses [26].

Reducing other error-producing conditions

To reduce other error-producing conditions, sensitivity and information content should be improved, alerts should not unnecessarily disrupt workflow and handling should be safe and efficient.

Sensitivity problems are common and a source of potential error [7,42,43]. Alerting features can be lacking, alerts can be turned off or bypassed, the knowledge database can be incomplete or not up to date, and patient data, like body weight and drug allergies, can be incomplete, not coded (free text), or incorrect. Examples of sensitivity problems are the absence of a check (on drug-laboratory interactions, on correct administration routes or on interactions that become important when stopping a drug), bypassing medication control by using free text, and the absence of new registered drugs and ad hoc preparations and their drug safety data in the drug database.

To improve sensitivity some relatively simple, albeit sometimes difficult to realize, measures can be taken. First, physicians should be encouraged to refrain from free text for drug name or dosage regimen [38]. Second, allergies and body weight should be entered consequently if the software can handle these data elements [38]. Furthermore, a regularly updated standardized drug database with allergies, interactions and other safety data is strongly recommended [11,27,44]. To further improve sensitivity and patient safety, technically more complex measures are necessary, like inclusion of laboratory data in alert generation [45].

Performance is dependent on information content of the knowledge database [46], alerting features and local customization [47]. A performance study with a standard set of prescriptions for 16 clinically important drug-drug interactions in commercial and proprietary community pharmacy software revealed a sensitivity (ability to correctly identify clinically important alerts) ranging from 0.44 to 0.88 and a specificity ranging from 0.71 to 1.00 [48]. A gold standard for calculation of sensitivity and specificity does not exist; the ratios depend on the test performed.

The alert information should be unambiguous, justified, and presented concisely to enable easy understanding and initial triage at a glance. Users contend that more information should be accessible; although such sporadically read information has not been proven to result in a higher response rate to reminders [28,39,49].

In CPOE systems with different alert levels, automatically overriding low-level alerts can result in motivation problems [14,19,22,23]. High specificity implies that only urgent serious alerts are shown. Alerts with lower levels of seriousness can be absent or shown nonintrusively [14,20,27].

Presentation of alternative actions on the same screen is subject to discussion. Advocates contend that such alerts are more effective in modifying physician behavior than alerts that only

suggest stopping intended actions. Advice on dose adjustment in renal insufficiency resulted in improved care, they argue; standard doses and frequencies are the most important way to help physicians in their work. It must be emphasized that these advocates are all from the same center [11,12,50-52]. Skeptics argue that the error risk will increase because physicians will not rely on their own cognition and that decision support cannot incorporate all medical knowledge or all unanticipated events and situations in health care [7,36,53,54]. Standardization of doses, frequencies, and route suggestions is thought to be an important source of erroneous orders and adverse events [36,54], although alerts suggesting controversial alternative orders were not acted on [55]. To help physicians in alert handling without giving complete alternative actions, concise information can be presented on normal doses, last measured drug serum levels or creatinine levels, and also other interacting drugs [45,54].

Turning off alerts without careful error management may impair patient safety [26,38]. CPOE system design should meet physicians' preferences as well as safety requirements. One option is to turn off particular alerts for particular specialist groups [26,27], for example, showing interaction alerts on ciclosporine and nephrotoxic drugs for all specialties except nephrology because specialists should have enough knowledge to prevent unsafe situations. However, if specificity is high, specialists do only receive unsolicited alerts if their prescriptions cause potential unsafe situations. A British study showed that 57% of prescribing errors were due to incorrectly executing an adequate plan because clinicians were busy or had been interrupted during routine tasks [34,35]. It is often not a knowledge deficit that results in errors, but oversight, distraction and forgetfulness [49]. Another option mentioned by users was to turn off alerts (centrally or automatically) if users perform well (if serum levels are being ordered and if good reasons for overriding are entered) [26]. Automatically preventing alerts [26] without informing physicians adds to nontransparency and does not seem desirable [38]. If well-performing physicians are allowed to change the alert presentation from intrusive to nonintrusive, they keep informed and perhaps are educated without unnecessary workflow interruptions [14,20].

CPOE systems may differ in their required actions to override alerts. In the system described by Nightingale, a penicillin allergy alert can never be overridden [13], but allergy information is often based on patient information that is incomplete or partly correct [14,16,38]. Some systems require entering a password or reason for overriding alerts that have the highest potential for causing adverse events [2,13,20,38], whereas other systems allow simply clicking away the alert.

Noninquisitive alerts guarantee efficient handling without disrupting workflow and are preferred [11,16,29,39,55]. However, if the only safety check can be done after entering extra information or a choice between two alternatives, sensitivity can be increased.

To improve efficient handling of alerts, computer interface design should be logical; the number of keystrokes, mouse clicks and screens should be kept as small as possible and speed be sufficient [11,22,26,28]. Detailed discussion of these technical, human computer interaction features falls outside of the scope of this paper.

Improving latent conditions

Safety of the alerting system may be further improved by influencing latent conditions, (pharmacy check, training and dependency), which have an indirect effect on the risk of a medication error. Alert overriding may be provoked by inappropriately high trust in the error-preventing actions of the pharmacy. Trust depends on the nature of the relation between professionals and can only be influenced over time.

If a complete pharmacy check of all orders is absent, pharmacists should manually check dosage regimens and drugs that cannot be checked by the system. Information that dose checking cannot be done by the CPOE system should be directed to the pharmacy.

Adequate formal training and improving information content may prevent misinterpretation of alerts. Frequently shown informative alerts may also result in a learning effect [28], but this has not been studied thoroughly. In a study of automated alerts for 2,000 drug combinations, physicians spending more time in the clinic (using the CPOE system) recognized more interacting drug-condition pairs and more contraindicated pairs, suggesting a learning effect [2].

Dependency can result from frequent alerts and pose a problem if users do not know the type of alerts the system is not checking for or if order check by supervisor or pharmacy is absent and not communicated to the users [2]. If physicians rely too much on computerized decision support, they may not reconsider medication profiles or identify medication problems by themselves. However, in one study, false positive alerts were not acted on [55]. Another study of alerts for incorrect dosing showed no difference in alert rate between experienced and inexperienced house staff suggesting that house staff was not dependent on the dosing assistance provided [17].

DISCUSSION AND CONCLUSION

Many CPOE systems contain decision support by integrated drug safety alerts to improve patient safety. Very little research has been done on overriding drug safety alerts. Eight studies showed 49-96% alert overrides, except for high-level overdose alerts, which are overridden in 27%. Standardization of alert levels is largely absent, making comparison of override rates difficult. The Dutch drug database contains a coding system for drug-drug interactions [56].

It should be emphasized that only unjustified overriding is problematic from a safety perspective. The authors advise entry of overriding decisions to gain deeper insight in (justified) overriding [20,22]. Alerting systems may contain error-producing conditions and customizing is necessary, regardless of the use of a commercially available or a manually constructed database [44]. Specificity or sensitivity should be increased as the result of consensus meetings between physicians and pharmacists [47].

This customization process may be time-consuming and difficult because increasing sensitivity increases the total number of alerts and probably the percentage of inappropriate alerts,

which decreases specificity. Required entry of reasons for overriding to prevent unintended overriding may result in an unacceptable time burden for physicians but gives useful information for system improvement [20,22,38]. Disallowance of order entry (hard stops) is unacceptable in the opinion of the authors, because decision support cannot replace the physicians' responsibility for the treatment of the patient [13]. It is questionable whether entering a simple password will prevent unintended overriding [13].

Many physicians complain about the poor signal-to-noise ratio and admit alert overriding because the alerts are not serious or irrelevant [2,22]. In studies on overriding, chart review did not reveal any adverse drug event in more than 97% of cases [15,19,20]. Furthermore, in daily practice adverse drug events often occur when the patient has moved to another point in the care chain, no longer within control for the physician(s) responsible for the event. Physicians believe that too many irrelevant alerts are presented and ask for turning off alerts 'they already know'. However, if specificity is high and alerts are only presented in potentially unsafe situations, specialists who already know them are not bothered by them. Furthermore, forgetfulness and oversight instead of a knowledge deficit are often the cause of generation of alerts and these problems can emerge in specialists as well as in residents [34,49]. A testable hypothesis is whether specialists receive fewer alerts on their specialty than residents.

Presenting correct alternative actions is very difficult because they should include the right alternative drug, dose and frequency for the patient's particular situation. The authors therefore propose to present concise information that can help physicians making a correct decision but to prevent selection of an alternative action with one click because indications may deviate from the indications on which the advice is based.

Decision support may result in physicians fully relying on the system and feeling safe if alerts are absent [2,7]. Sensitivity problems can be divided between absence of alerts within a particular alert feature and lacking alert features. Today, decision support on genetic profiles influencing drug-drug interaction effects, is often lacking and physicians will not expect alerts of this type. If some type of alerting is present, physicians will have trust in complete decision support of that type, and increasing sensitivity as well as manually checking defensive gaps in the alerting system should achieve this. These gaps may change over time because of local customization and should result in a change in the pharmacy check to ensure patient safety. Which factors influence this pharmacy check is not clear.

The literature summarized in this paper focuses on the magnitude of overriding drug safety alerts, reasons and causes for overriding in general, effects of overriding, and suggestions for useful alerts. It is still not clear whether interactions on administration time, the level of seriousness, and the alternative action should be shown to the prescribing physician. The following hypotheses could be tested. Directing alerts on administration time to nurses or pharmacy technicians reduces the number of administration errors. Presentation of different levels of seriousness increases the override rate compared to one level of seriousness. Presentation of an alternative increases the number of unjustified cancellations or changes of order.

Before testing these hypotheses, it would be useful to gain insight in the cognitive processes playing a role when physicians are confronted with different types of alerts. None of the studies addressed this aspect of alert overriding. Rasmussen describes three levels of human performance (skill-, rule-, and knowledge-based behavior) and three corresponding ways in which information is perceived, depending on intentions and expectations of the receiver [57]. It is not clear which level of human performance is used in interpretation and handling of drug safety alerts and which factors determine this performance level. Understanding reasons for and causes of overriding in particular cases is necessary for development of effective alerting systems that are acceptable to users.

Decision support in CPOE can be a good tool to improve patient safety but can also hamper patient safety if badly designed. The authors have argued how alert overriding can be understood with the help of Reason's model of accident causation and how decision support in CPOE might be designed to improve patient safety.

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Chapter 2.2

Drug safety alert generation and overriding in a large Dutch University Medical Center

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ABSTRACT

Purpose: To evaluate numbers and types of drug safety alerts generated and overridden in a large Dutch University Medical Center.

Methods: A disguised observation study lasting 25 days on 2 internal medicine wards evaluating alert generation and handling of alerts by prescribing physicians. A retrospective analysis was also performed of all drug safety alerts overridden in the hospital using pharmacy log files over 24 months.

Results: In the disguised observation study on internal medicine wards 34% of the orders generated a drug safety alert of which 91% were overridden. The majority of alerts generated (56%) concerned drug-drug interactions (DDIs) and these were overridden more often (98%) than overdoses (89%) or duplicate orders (80%). All drug safety alerts concerning admission medicines were overridden.

Retrospective analysis of pharmacy log files for all wards revealed one override per 5 prescriptions. Of all overrides, DDIs accounted for 59%, overdoses 24% and duplicate orders 17%. DDI alerts of medium-level seriousness were overridden more often (55%) than low-level (22%) or high-level DDIs (19%). In 36% of DDI overrides, it would have been possible to monitor effects by measuring serum levels. The top 20 of overridden DDIs accounted for 76% of all DDI overrides.

Conclusions: Drug safety alerts were generated in one third of orders and were frequently overridden. Duplicate order alerts more often resulted in order cancellation (20%) than did alerts for overdose (11%) or DDIs (2%). DDIs were most frequently overridden but only a small number of DDIs caused these overrides. Studies on improvement of alert handling should focus on these frequently-overridden DDIs.

INTRODUCTION

Drug safety alerts in computerized physician order entry systems (CPOEs) are meant to improve patient safety. The small amount of literature on drug safety alert overriding shows that these alerts are frequently overridden [1-12]. If the burden of alerts is too high, alert fatigue may cause physicians to override both important and unimportant alerts, so undermining this safety measure [13]. Measures to decrease the burden of alerts are: increasing alert specificity, directing alerts to other people in the workflow, clear and concise alert texts, and safe and efficient alert handling, among others [13]. Insight into the generation and overriding of drug safety alerts may reveal potential problems of alert fatigue and help focus on areas for improvement of the alerting system [2].

The aim of this study is to gain an insight into alert generation and overriding in a large Dutch university hospital. The questions to be answered in this study are:

1. How many and what type of drug safety alerts are generated?
2 What types of drug safety alerts result in order cancellation or adjustment?
3. Is there any difference in handling of drug safety alerts for admission medicines and new orders?
4. How many and what types of drug safety alerts are overridden?
5. How many and what type of drug-drug interactions (DDIs) are most frequently overridden, with respect to level of seriousness, DDI category and individual DDI alerts?

Disguised observation and analysis of overridden alerts were used to answer these questions.

BACKGROUND

All CPOEs used in Dutch hospitals use the Dutch drug database G-standard, which contains safety information on all drugs registered in the Netherlands, including DDIs, duplicate orders, and overdoses [14,15]. It also provides standardized alert texts [15]. The seriousness index for DDIs has six categories (A through F), in increasing level of seriousness. In this study 3 categories of seriousness are used: low level (comprising category A and B), medium level (C and D), and high level (E and F). DDIs that have not yet been assigned a seriousness index are categorized as unknown. 23% of alerts in the G-standard are low level, 50% are medium and 27% are high level.

Categorization into levels of seriousness does not show what actions should be performed upon alert presentation. So we divided appropriate responses into 8 groups, using recommendations from the standardized alert texts: 1) monitor clinical chemistry data, 2) monitor drug serum level, 3) monitor blood pressure or electrocardiogram, 4) adjust administration time, 5) avoid serious consequences (gastric bleeding, serotonin syndrome, myopathy, nephrotoxicity), 6) increase drug dose, 7) decrease drug dose, 8) other (e.g., advise the patient, add ritonavir as a booster). It is assumed that alert specificity would be improved by linking alert generation (and suppression)

to clinical chemistry data, drug serum levels, or clinical effect-related patient parameters [13]. To decrease the burden of alerts on the physician, nurses could probably handle time-dependent DDI alerts [13]. The other categories probably always require handling by physicians.

METHODS

Setting

Erasmus University Medical Center in Rotterdam, the Netherlands, a 1,237 bed tertiary hospital, has been using CPOE for drug prescriptions (Medicatie/EVS®, Leiden, the Netherlands) on all inpatient wards except for intensive care units since March 2005 [6]. Physicians and midwives exclusively enter prescriptions, as nurses are legally not allowed to prescribe drugs. Drug safety alerts for DDIs, overdoses and duplicate orders are based on the Dutch drug database and are shown intrusively [15]. Alerts show the drugs involved, their dosage regimen, and an explanation including a recommendation [15]. Overridden alerts are logged for pharmacy review. Alerts that result in changed or cancelled prescriptions with concomitant alert annulment are not logged.

Disguised observation

At present, pharmacy logs only show prescriptions for which an alert was generated and overridden. Logs do not reveal prescriptions that are cancelled when an alert is presented at order entry. In order to study this part of alert handling too, disguised observation during order entry was necessary. Protocol evaluation by the local ethics committee was not required, as the study did not include any change in physicians' behaviour. The real goal of the observation was not stated so as not to influence prescriber behaviour. The announced goal was to study CPOE use for possible improvements. Sample size was calculated on the assumption that one third of prescriptions generate an alert and that 90% of alerts generated are overridden [6]. It was calculated that a sample size of at least 450 prescriptions was required to collect 15 alert annulments, resulting in an observation period of 15 days. The study took place on 2 internal medicine wards with 3 residents per ward over 13 and 12 weekdays respectively. In the five-week study period a trained pharmacy student was present during day shifts (from 9.00 to 17.00) in the residents' room, where residents electronically prescribe drugs. The residents indicated when they were about to enter orders. Observations of order entry were written down on a data collection form and checked with the pharmacy log files for these wards.

Retrospective analysis of pharmacy log files

Separate lists of logged overrides of DDIs, overdoses and duplicate orders were printed out over 24 months, counted manually per month and related to the number of prescriptions. DDI overrides over 8 months were categorized by level of seriousness as provided by the Dutch drug database, and by the 8 response groups.

RESULTS

Disguised observation study

Six residents on 2 internal medicine wards entered 515 prescriptions during observation hours (6.9 orders/resident per day), of which 31% concerned admission medicines. 176 orders generated a drug safety alert (34%). Admission medicines generated fewer alerts (38/159=24%) than the newly prescribed orders (138/356=39%). The majority of the alerts generated (56%) were DDIs, 15% concerned overdose and 29% were due to therapeutic duplication.

In total, 161 of the 176 alerts were overridden (91%), all 38 alerts on admission medicines were overridden, whereas new prescriptions resulted in 89% overriding. DDIs were overridden more often (98%) than overdoses (89%) or duplicate orders (80%) (Table 1). Of all alert overrides 60% were DDIs, 15% overdoses and 25% duplicate orders. During the five weeks of the study 877 orders were entered on the wards studied, of which 59% could be observed during normal working hours, the remainder being prescribed outside the day shifts. The percentage of prescribed orders associated with overrides was 31% (161/515) for the wards observed during the 5-week study period.

Table 1 Handling of drug safety alerts in disguised observation study

All orders

	Alerts generated	Alerts overridden	Orders cancelled	Orders adjusted
Total	176	161 (91%)	14 (8%)	1 (0.6%)
Drug-drug interactions	98	96 (98%)	2 (2%)	
Overdose	27	24 (89%)	2 (7%)	1 (4%)
Duplicate orders	51	41 (80%)	10 (20%)	

Clinical orders (admission medicines excluded)

	Alerts generated	Alerts overridden	Orders cancelled	Orders adjusted
Total	138	123 (89%)	14 (8%)	1 (0.7%)
Drug-drug interactions	76	74 (97%)	2 (3%)	
Overdose	20	17 (85%)	2 (10%)	1 (5%)
Duplicate orders	42	32 (76%)	10 (24%)	

DDI alerts for admission medicines were predominantly of a lower level of seriousness (55% low, 27% medium, 9% high level) than they were for newly prescribed medicines (26% low, 43% medium, 25% high level).

Physicians generally entered all admission medicines for one patient in one session generating 1.52 (SD 1.71) alerts, whereas the figure was 0.61 (SD 1.02) per patient per session for hospitalized patients.

Drug safety alerts that did not result in overriding but in annulment by order cancellation or adjustment are shown in Table 2. Duplicate orders for both identical and comparable drugs were equally present in this annulment category. One prescription for cotrimoxazole was cancelled after a high-level alert was generated for possible QT prolongation due to combination with

Table 2 Alerts not overridden in the disguised observation study

Alert type	Alert description	Action
Duplicate order	Acetaminophen (2 orders)	New order cancelled
	Colchicine (2 orders)	New order cancelled
	Formoterol inhalation (2 orders)	New order cancelled
	Esomeprazole – pantoprazole	New order cancelled
	Cefuroxim – coamoxiclav	New order cancelled
	Piperacillin/tazobactam - coamoxiclav	Current order stopped
	Piperacillin/tazobactam - amoxicillin	Current order stopped
	Nadroparine-acenocoumarol	Current order stopped
	Dexamethasone- hydrocortisone	Current order stopped
	Beclometasone/formoterol –formoterol	Current order stopped
Overdose	Acetaminophen (due to duplicate order)	New order cancelled
	Nystatin suspension	New order cancelled
	Metoclopramide	Order adjusted
Drug-drug interaction	Cotrimoxazole – amitriptyline (5088, level E; QT prolongation, monitor ECG)	New order cancelled
	Insulin – carvedilol (299, level D; masks hypoglycemia, monitor glucose)	New order cancelled

amitriptyline but reinstated after examination of the electrocardiogram. Table 3 shows overridden alerts categorized by appropriate response. In 45.8% of the overrides, clinical chemistry or drug serum levels data could be requested by which the alert could have been assessed. Time-dependent DDIs that could probably be directed to nurses accounted for 22.9% of the overrides.

Table 3 Drug-drug interactions overridden in the disguised observation and retrospective studies, grouped by appropriate response

DDI category	Disguised observation study Percentage	Retrospective study Percentage
Monitor clinical chemistry data	42.7	31.7
INR	10.4	13.4
Glucose	18.8	9.9
Potassium	13.5	8.1
Monitor drug serum levels	3.1	4.7
Monitor blood pressure/ECG	22.9	34.9
Sequence-dependent hypotension	10.4	21.5
QT prolongation	5.2	6.8
Adjust administration time	22.9	8.8
Avoid serious consequences	6.3	15.8
Gastric bleeding	3.1	8.8
Nephrotoxicity	2.1	4.9
Myopathy	1.0	1.3
Increase drug dose	1.0	3.1
Decrease drug dose	1.0	1.0
Other (advise the patient, add ritonavir as a booster)	0	0

DDI = drug-drug interaction, INR = international normalized ratio, ECG = electrocardiogram

Retrospective analysis of pharmacy log files

Analysis of overridden drug safety alerts in the general hospital of Erasmus University Medical Center over 24 months revealed 74,967 alert overrides in 371,261 prescribed orders. One-fifth of the prescribed orders (20.2%) resulted in an alert override. Figure 1 shows the percentage overrides per prescription over 24 months; DDI overrides were most abundant (11.8%). Of all alert overrides 59% were DDIs, 24% were overdoses and 17% were duplicate orders.

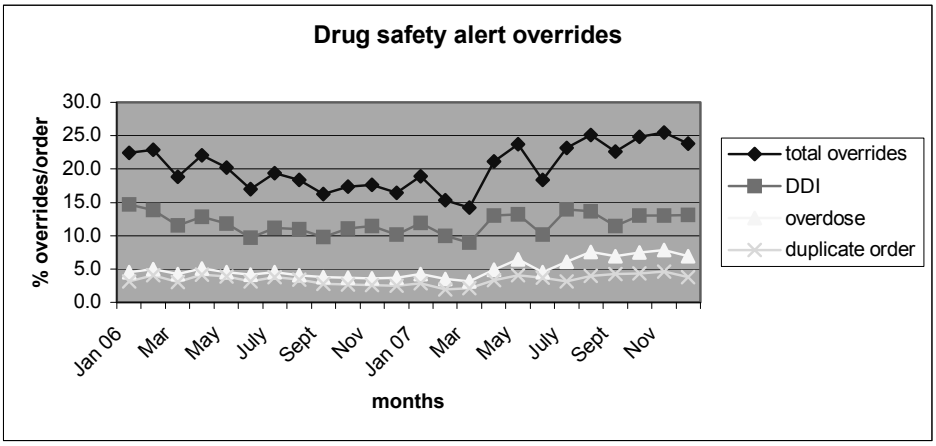

Figure 1 Drug safety alert overrides over 24 months

A closer analysis of overridden DDIs revealed that medium-level alerts were most frequently overridden (54%) compared to low-level (22%) or high-level alerts (19%) (Table 4). These percentages are comparable to the frequency distribution of available alerts in the Dutch drug database (23%, 50% and 27% for low, medium and high-level alerts respectively).

In this retrospective study of overridden alerts, serum level measurements were recommended in 36.4% of the overrides and 21.5% concerned hypotension due to the combination of ACE inhibitors and diuretics, which is only relevant in case of ACE inhibitors started in a patient already taking diuretics (Table 3).

The average number of different alerts was 91 per month. The 20 most frequently overridden DDIs are shown in Table 5. These 20 alerts (22% of the generated alerts) accounted for 76% of all overrides.

Table 4 Level of seriousness of overridden drug-drug interactions in retrospective study

Level of seriousness	Percentage
Low level (AB)	22.4
Medium level (CD)	54.5
High level (EF)	19.3
Unknown	3.8

Table 5 Top 20 overridden drug-drug interaction alerts
DDIs are presented in decreasing order of overrides per month

DDI database code	DDI description	Average number of overrides per month	Required action
19	ACE inhibitors and diuretics	281	Check sequence of prescribing; DDI only relevant if angiotensin-converting enzyme inhibitor is added to patient on diuretics (sequence-dependent hypotension).
566	Coumarins and antibiotics (except cotrimoxazole, metronidazole, cefamandol)	114	Monitor INR
2046	NSAIDs (except COX-2 inhibitors) and corticosteroids	107	Add gastric protection to avoid gastric bleeding
302	Selective beta-blockers and insulin	105	Monitor glucose
5088	QT interval-prolonging drugs and QT interval-prolonging drugs (except erythromycin, clarithromycin, voriconazole)	104	Monitor QT interval
35	ACE inhibitors and potassium-sparing diuretics	91	Monitor potassium
1228	AT receptor antagonists and diuretics	60	Check sequence of prescribing; only relevant if angiotensin antagonist is added to patient on diuretics (sequence-dependent hypotension)
78	Alpha-blocking drugs (for benign prostate hyperplasia) and beta-blockers/ calcium channel blockers	47	Monitor blood pressure
2135	Bisphosphonates and antacids/iron/ calcium	44	Check for required time interval between drug administrations (time-dependent DDI)
3964	Beta-blockers and oral hypoglycemic drugs	33	Monitor glucose
1066	Potassium and potassium-sparing drugs	30	Monitor potassium
272	Beta-blockers and NSAIDs	27	Monitor blood pressure
531	Coumarins and amiodarone/ propafenone	26	Monitor INR
299	Non-selective beta-blockers and insulin	26	Monitor glucose
1465	Tacrolimus and enzyme inhibitors	26	Monitor drug serum level (of tacrolimus)
1155	Diuretics and NSAIDs	24	Monitor blood pressure
3433	Thyreomimetics and iron/calcium	24	Check for required time interval between drug administrations (time-dependent DDI)
5347	Metoprolol and CYP2D6 inhibitors	23	Monitor blood pressure
27	ACE inhibitors and NSAIDs	22	Monitor blood pressure
3360	NSAIDs (except COX-2 inhibitors) and selective 5HT reuptake inhibitors/ trazodone	17	Add gastric protection to avoid gastric bleeding

DISCUSSION

In the disguised observation study alerts were generated in 34% of all orders, which is in line with the 36% observed by Kalmeijer in 2001 with an earlier version of the same CPOE system [6,13]. Other CPOEs have shown lower alert generation rates of 7%, 11%, 11%, 14% and 30% [4,5,7,9,12]. It is not clear whether alert generation in one third of prescriptions is too high, as alert numbers appear to be less important than other factors such as timeliness and good signal-to-noise ratio [16].

Admission medicines generated fewer alerts than new prescriptions, which can be explained by the fact that increasing the number of orders (which generally occurs during hospital stay) exponentially increases the number of drug combinations and consequently the likelihood of an (duplicate order or DDI) alert being generated. An explanation for the increased proportion of lower seriousness alerts cannot be given.

The observed override rate of 91% was in line with the literature, although comparison of studies is hampered by differences in number and type of drug safety alerts [1-9,11-13]. Bates et al. propose a much lower override rate of less than 40% for strongly action-oriented suggestions, but it is not clear whether the overridden alerts in our study belong to this category [17]. Shah showed a low override rate of intrusive alerts of 33%, because of noninterruptive presentation of the majority of alerts [10]. Although an override rate of 91% is high, the remaining 9% of the alerts resulted in action (order cancellation or adjustment). Furthermore, alerts that were overridden could have led to the preferred action of increased monitoring of drug serum levels, clinical chemistry data, or ECG recording, but this has not been studied. We may therefore conclude that alerts are acted upon, and should not be considered useless.

Although a higher override rate was expected for alerts on admission medicines as compared to medication started in hospital, residents in internal medicine overriding *all* admission alerts was an unexpected finding. Internists were thought to be more pharmacotherapy-minded than surgeons and more vigilant in drug safety alert handling. However, the level of seriousness was much lower for the DDIs of admission medicines than for clinically started drugs and only 38 admission medicines overrides were observed. The higher number of alerts generated per order entry session could have played a role in developing alert fatigue. Another explanation is that the residents (whether or not justifiably) relied on former alert checking by physicians starting the treatment or by community pharmacists delivering the medicine. On the other hand, if physicians systematically override all admission alerts, this poses the question whether physicians or pharmacists should perform admission medicines review. Interventions of clinical pharmacists to solve or prevent drug-related problems are accepted and acted on to a large degree [18]. These interesting findings should be further evaluated in a larger scale study.

In the retrospective analysis of overridden drug safety alerts, the fact that generated alerts resulting in order cancellation were not logged hampered interpretation of results. The percentages of overridden alerts per prescription presented in Figure 1 suggest increased overriding

in the latter part of 2007, but this cannot be proven statistically as numbers of generated alerts cannot be extracted from the CPOE and are therefore unknown. The level of seriousness and response group of the generated alerts are also unknown and it cannot be concluded which category has a higher override rate. The frequency distribution for seriousness of available DDI alerts in the Dutch drug database does not match the frequency distribution of alerts generated either. Software vendors are therefore kindly requested to log both generated and overridden alerts to enable override rates to be monitored and areas for improvement of the alerting system to be targeted [11].

The high override rate for DDIs and the fact that 20 individual DDIs comprised 76% of the DDI override rate suggest that these alerts may have a high false positive rate. These alerts should be further evaluated for possible improvements in specificity, information content or handling efficiency. In more than one-third of overridden alerts the prescriber was able to react by requesting clinical chemistry data or drug serum levels. If alert generation were to be linked to the laboratory system, measured serum levels could be used for alert suppression, thereby increasing alert specificity [15]. Time-dependent DDIs can probably be directed to nurses and unnecessary sequence-dependent hypotension alerts can probably be prevented by CPOE adjustments.

The percentage of prescriptions that contained overrides in the disguised observation study on internal wards was 31% as compared to 20% in the retrospective study on all wards of the general hospital. This may be due to more alerts per order being generated, which is most likely, and/or a higher override rate in the internal medicine department. Duplicate order overrides were also more frequently observed in the disguised observation study on internal wards (25%) than in the retrospective study (17%), which can be explained by the fact that internists generally prescribe more drugs, which increases duplicate order alert generation.

The differences in action-oriented grouping can also be explained by the fact that disguised observation was performed on internal medicine wards with a higher proportion of patients taking glucose-lowering drugs, drugs that affect the potassium level or drugs that result in time-dependent DDIs (levothyroxine and bisphosphonates). 23% of overridden alerts in the disguised observation study involved time-dependent DDIs; directing those alerts to other people in the workflow, such as nurses, could further reduce the number of alerts to be handled by the physician [15].

Strengths and weaknesses

The study had some limitations. A major validity concern in the disguised observation study is a potential effect of the observer on the observed physicians. Generally, people resume their normal behaviour after about 1-3 hours of observation [19]. In this study each resident was observed over 3 weeks, and the observer was a trained pharmacy student who would not be considered a threat to the residents. An observer effect is therefore assumed to be negligible.

One pharmacy student had to observe three residents who were present in one room. This could have led to simultaneous prescribing. Fortunately, the number of prescriptions/day was

low, the residents indicated when they were about to enter orders and all orders made were observed.

This study did evaluate actual overriding behaviour under normal circumstances but did not cover reasons for, or causes of, overriding. Other types of study are necessary to evaluate this.

Observation was limited to one CPOE system in one hospital, 25 days during normal working hours, 2 wards of 1 specialty, and 6 residents. The average number of 6.9 orders per resident per day was less than the expected 10-15. It is assumed that prescription and alert numbers are even lower for surgical specialties and that disguised observation on surgical wards would have resulted in less information on alert and override rates. It can be questioned whether observation of other physicians from internal medicine, or from other specialties, would show similar results. The scope of this study however was not to identify differences between specialties, but to get an insight into the number and type of frequently overridden drug safety alerts.

CONCLUSION

One-third of all orders prescribed on internal medicine wards resulted in drug safety alert generation. Overriding was very frequent (91%), especially for DDIs (98%). Duplicate order alerts resulted in order cancellation in 20% of alerts. Drug safety alerting cannot be stated to be useless, however. The remaining 9% of alerts resulted in order adjustment or cancellation, and possible increased monitoring due to alerts was not measured. Retrospective analysis of overridden drug safety alerts revealed that a small number of 20 DDIs caused the majority (76%) of all overrides, and that it was possible for doctors to respond to 36% of overridden alerts by requesting drug serum level or clinical chemistry data monitoring. These alerts should be studied further in order to improve the alerting system, for example by improving alert specificity, information content or alert handling.

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Chapter 2.3

Understanding handling of drug safety alerts: a simulation study

Heleen van der Sijs, Teun van Gelder, Jos Aarts, Arnold Vulto, Marc Berg

ABSTRACT

Objective: To study correctness of drug safety alert handling and error type in a computerized physician order entry (CPOE) system in a simulated work environment.

Design: Disguised observation study of physicians entering 36 orders of predefined patient cases with 13 different drug safety alerts in a CPOE. Structured interviews about how the generated drug safety alerts were handled in the simulation test and resemblance of the test to the normal work environment.

Measurements: Eighteen residents (12 from internal medicine and 6 from surgery) were observed and interviewed. Handling and reasons for this were scored for correctness and error type.

Results: Thirty percent of alerts were handled incorrectly, because the action itself and/or the reason for the handling were incorrect. Sixty-three percent of the errors was categorized as rule based and residents in surgery used incorrect justifications twice as often as residents in internal medicine. They often referred to monitoring of incorrect substances or parameters. One alert presented as a second alert in one screen was unconsciously overridden several times. One quarter of residents showed signs of alert fatigue.

Conclusion: Although alerts were mainly handled correctly, underlying rules and reasoning were often incorrect, thereby threatening patient safety. This study gave an insight into the factors playing a role in incorrect drug safety alert handling that should be studied in more detail. The results suggest that better training, improved, concise alert texts, and increased specificity might help. Furthermore, the safety of the predefined override reason 'will monitor' and double alert presentation in one screen is questioned.

INTRODUCTION

Overriding of drug safety alerts in computerized physician order entry systems (CPOEs) is very common and occurs in 49-96% of cases [1]. However, frequent overriding may cause alert fatigue, important alerts being overridden along with unimportant ones, so impairing patient safety. Research into overriding has been focused on the extent of overriding, reasons and causes for overriding in general, effects of overriding and suggestions for useful alerts [1]. Studies on the role played by cognitive processes in overriding drug safety alerts are lacking [1]. It is not clear which cognitive level is used in interpretation and handling of drug safety alerts, which kind of errors are made and which factors determine these processes. Understanding the reasons for, and causes of, overriding in particular cases is necessary for the development of effective alerting systems that are safe and acceptable to users [1].

The aim of this study is to gain an insight into errors occurring in drug safety alert handling. The research questions are:

1. How many, and which type of, errors are made in handling drug safety alerts?
2. Are there any signs of alert fatigue or dependency on the alerting system?

BACKGROUND

The handling of drug safety alerts can be divided into several steps: the alert has to be read and understood, the consequences of the intended plan have to be weighed, and the intended action has to be performed [1]. In each step different types of errors can be made.

Reason divides human errors into slips, lapses and mistakes [2,3]. Slips are acts not intended nor attended; errors in which the right intention is incorrectly carried out, for example clicking the override button instead of the cancellation button [4]. Lapses are errors of omission, for example forgetting to place a remark in the order that drugs should be administered separated by an interval of 2 hours. Slips and lapses are examples of execution failures. Mistakes are made when the intended action is wrong, which may be due to misinterpretation of the situation or to errors in planning an intended action, for example by applying wrong rules. Mistakes are categorized as problem-solving failures [2]. If Reason's model of accident causation is applied to drug safety alert handling, three types of active failures can be discerned: ignoring alerts, misinterpretation and wrong selection [1].

Rasmussen identifies three levels of human performance in information processing: skill-based (SB), rule-based (RB), and knowledge-based (KB) behavior [5]. SB performance takes place without conscious attention or control and the person generally does not know why he acted in a particular way or on what information he based his action. In RB behavior the actor uses rules of the type 'if-then', which have been derived empirically or have been learned from textbooks or other persons. At the KB level, the person resorts to functional reasoning after

pre-existing solutions have failed, making a plan with different scenarios, based on the environment and ultimate goal [5].

This SRK framework is a basic model often used in cognitive psychology. The framework describes how individuals process information and make decisions on their own [3] and which level of cognitive control is guiding their behavior [6]. The SRK framework is often used as a tool for *post hoc* analysis of accidents. Errors made on different cognitive levels require different interventions to prevent them [4,6]. Therefore, insight into the error type is a prerequisite to developing suitable interventions for error reduction.

Physicians handling drug safety alerts have to process the alert information and to decide whether alert overriding or annulment is appropriate and whether additional information or monitoring is required. It is likely that errors are being made, because alert override rates are high, even if only alerts that require action are generated [1,7]. As alert handling is generally performed individually, the SRK framework seems to be an appropriate model.

People intuitively prefer handling strategies that depend on sequences of simple operations instead of switching to a higher performance level requiring more mental energy [2,5]. Preprogrammed SB behavior is therefore preferred to RB behavior. SB errors are easily made because of inattention, but are generally easily detected when the feedback of the output fails to match the expected feedback [2,4].

Similarly, RB behavior is preferred to KB behavior. RB errors can be divided into misapplication of good rules, application of bad rules, and failure to apply good rules. Rules that have frequently been employed successfully in the past are extremely strong ones that are easily misapplied even if the circumstances no longer warrant their use [2,4]. The two error-prone mechanisms that play a role in this are similarity matching, deciding that one situation more or less resembles another, and frequency gambling, using the most frequently-used successful rules [2-4]. Performance at the KB level is more error prone than at the RB and SB level, because the workspace for problem solving is limited and information acquisition and integration can fail in many different ways [2,4]. For example, one could give attention to the wrong features, give undue weight to facts that come readily to mind, to evidence that favors the chosen course of action, or to perceived causality [2]. RB- and KB-based errors are generally not easily detected because actions are performed according to plan [2].

With decreasing familiarity with the environment or the task the person resorts to KB instead of SB behavior [2] and consequently, the performance level is influenced by both the level of training and the experience with the situation or the alert.

METHODS

Setting

The Erasmus University Medical Center in Rotterdam, the Netherlands is a 1,237-bed academic medical center that started introducing CPOE in December 2001. Since March 2005 all inpatient wards, intensive care units excluded (1,107 beds), have been using the Windows-based CPOE system Medicatie/EVS® (iSOFT, Leiden, the Netherlands) [8].

Test development

A simulation test was developed with 6 patient cases, 36 orders and 13 drug safety alerts of different types (2 duplicate orders, 8 drug-drug interactions (DDIs), and 3 overdoses) and different familiarity. Seven alerts needed to be overridden, 6 required order adjustment. The percentage alerts per order (36%) and the relative number of DDI alerts (62%) were comparable to those encountered during daily drug prescribing in the hospital [7-9]. One duplicate order (DO) was relevant, the other irrelevant. One DDI was irrelevant, the others required monitoring of glucose serum level, international normalized ratio (INR), recording an electrocardiogram (ECG), prescribing a gastro-protective drug, adjusting administration times, or lowering the dose of captopril. This latter frequently-overridden alert is a sequence-dependent alert that is only relevant if the angiotensin-converting enzyme inhibitor is started in a patient already using diuretics, which is rare but is the case in this study. All three overdose alerts were relevant and were due to a wrong unit (milligram instead of microgram for a drug known for its small therapeutic range) or to confounding the dose per administration and per day for lesser-known drugs (twice). The alert recommendation for one of these overdose alerts was correct and the other was incorrect. The test is presented in Table 1. Brand names as well as generic drug names were used to achieve similarity with normal medical information in handovers.

Data collection

All residents of internal medicine and surgery were invited by email to participate in a test to study user friendliness of the CPOE, which would take three quarters of an hour and would be rewarded by 25 euros in gift vouchers. Residents who were willing to participate and had at least 3 months' experience with the CPOE were selected for this study.

For safety reasons, the test mode of the CPOE had to be used for order entry in this study. Because this test mode is not available on the wards, the test took place in the hospital pharmacy. The patient cases were presented to the physician in a patient handover. The physician could ask questions for clarification. Thereafter the physician had to enter the orders into the CPOE in a noisy atmosphere under time pressure. The physician was distracted by paging and/or by stressing the limited time available, simulating the normal work environment on the ward.

During order entry the physician was observed using an observation form. After order entry, the physician was interviewed about the observed handling of the drug safety alerts generated,

Table 1 Patient cases and drug safety alerts generated

Case	Order	Dose	Alert	Comment on alert
1	Woman 61 years old (1.65 m, 60 kg), with diabetes mellitus type 1 has been admitted to the intensive care with liver failure and has undergone a liver transplantation. Now she has been moved back to the ward.			
	Prograft (tacrolimus)	5 mg twice daily po		
	Cellcept (mycophenolate mofetil)	1000 mg twice daily po	Duplicate order (immunosuppressive agents) (tacrolimus–mycophenolate mofetil)	Irrelevant duplicate order alert: combination is desired after transplantation.
	Prednisolone	20 mg twice daily po		
	Cotrimoxazole	480 mg once daily po	DDI 5088 QT prolongation by combination of two QT-prolonging agents (tacrolimus-cotrimoxazole)	High-level DDI, ECG monitoring possible, cotrimoxazole unlikely to cause Torsades de Pointes, tacrolimus has possible risk of Torsades de Pointes. Common combination after transplantation and QT prolongation not relevant in low dose cotrimoxazole in patients without congenital QT prolongation. Cotrimoxazole necessary to prevent *Pneumocystis carinii* infection.
	Novorapid (insulin aspart)	06:00 am 8 IU 02:00 pm 12 IU 10:00 pm 10 IU prn 4 IU extra if glucose >15	(Duplicate order)	(Alerts can be prevented by prescribing correctly, complex order)
	Bisoprolol	10 mg once daily po	DDI 0302 Masking of hypoglycemia by selective beta-blockers (insulin aspart–bisoprolol)	Low-level DDI, common combination and known DDI. Only relevant in high doses of beta-blockers. Regular glucose monitoring takes place in hospital setting.
	Nexium (esomeprazole)	40 mg once daily po		
2	Man, 70 years old (75 kg) with hypertension, for which he has already been treated at home. The patient has been admitted with edema and has suspected heart failure. He has a urinary infection and heartburn. Home medication already entered in the CPOE: furosemide 1dd 40 mg, acenocoumarol according to thrombosis service schedule, simvastatin 40 mg at night.			
	Captopril	25 mg thrice daily po	DDI 0019 Severe hypotension when diuretics are added to ACE inhibitors without dose adjustments (furosemide-captopril)	Medium-level DDI. Severe hypotension when ACE inhibitors are started in this dosage in a patient already taking diuretics. Dose of captopril should be lowered to 6.25mg.

Table 1 continued

Case	Order	Dose	Alert	Comment on alert
	Digoxin	250 mg once daily po	Overdose (maximum daily dose is 250 microgram)	Serious overdose, factor 1000 (mg instead of microg).
	Bactrimel (co-trimoxazole)	960mg thrice daily po	DDI 0590 Prolongation of INR by co-trimoxazole (acenocoumarol-cotrimoxazole)	Medium-level DDI. Alternative antibiotic advised for treatment course. If combined, frequent monitoring of INR required and dose adjustment of the anticoagulant accordingly.
	Antagel (algeldrate + Mg hydroxide)	10ml thrice daily po	DDI 0787 Decreased absorption when administered at same time (digoxin-antacid)	Low-level DDI. Interaction that can be prevented by adjusting administration times or placing a remark in the order that the drugs should be administered separated by an appropriate time interval. Digoxin should be administered at least 2 hours before or 4 hours after antacid.
3	Woman, 75 years old has fallen at home and therefore admitted to hospital. She has a lot of pain. She has suffered from depression for a long time and has hypertension.			
	Seroxat (paroxetine)	20mg once daily po		
	Eucardic (carvedilol)	6.25 mg once daily po		
	Acetaminophen	1 g 4 times daily po		
	Diclofenac	25mg thrice daily po, 1 tablet extra prn, stop after one week	DDI 0272 Hypotensive effect of beta-blockers caused reduced by NSAID. Heart failure may worsen. (carvedilol-diclofenac)	Medium-level DDI. In hypertension only relevant for long-term use of NSAIDs (not for one week's treatment). Relevant in case of heart failure.
			DDI 3360 Increased bleeding risk (paroxetine-diclofenac)	Medium-level DDI. Addition of gastric protection (proton pump inhibitor) recommended for long-term use of the combination, elderly patients, gastric ulcer in history, high dose of NSAID and concomitant corticosteroid use.
	Tramadol slow release	100mg once daily	DDI 4227 Serotonin syndrome (paroxetine-tramadol)	High-level DDI. Alternative analgesic advised. However patient has already been given diclofenac and acetaminophen in maximum dose. If combined, nurse should be informed to alert physician in case of muscle rigidity, fever, confusion and/or agitation.

Table 1 continued

Case	Order	Dose	Alert	Comment on alert
4	Woman, 46 years old (70 kg), known to suffer from SLE (systemic lupus erythematosus) has been admitted recently with an exacerbation of SLE with swollen joints and a lot of pain.			
	Hydrocortisone	20mg morning, 10mg evening oral		
	Hydroxychloroquine	400mg twice daily po	Overdose (maximum daily dose is 400mg)	Serious overdose. Adverse events after prolonged use of high doses. Normal doses in SLE 400 mg daily in 2 doses. Maximum dose in SLE 600mg daily. Lesser known drug, prescribed infrequently.
	Celecoxib	20mg once daily po		
	Tramadol retard	100mg once daily po		
	Methylprednisolone	1 g once daily for three days iv	Duplicate order (corticosteroids) (hydrocortisone–methylprednisolone)	Combination of corticosteroids is undesirable and hydrocortisone should be stopped during the methylprednisolone course. The risk of not restarting hydrocortisone may not outweigh the benefit of stopping it and the amount of corticosteroid due to hydrocortisone is negligible compared to that of methylprednisolone.
5	Man, 41 years old, coming from the outpatient pain clinic with neuropathic pain.			
	Amitriptyline	50 mg twice daily po		
	Valproic acid	900 mg thrice daily po	Overdose (maximum dose = 600 mg/dose, 2000 mg/day)	Rather serious overdose. Maximum dose for neuropathic pain 1000 mg/day, normally 300mg thrice daily. Maximum dose for epileptic seizures 2500mg daily, based on serum levels. Serum level measurements not useful in neuropathic pain.
	Lyrica (pregabalin)	300 mg twice daily po		
	Cremor capsicum	Bid applied thinly		

Table 1 continued

Case	Order	Dose	Alert	Comment on alert
6	Man, 77 years old (70 kg) has been moved from another university hospital to our hospital (wish of the family). The patient has renal failure and had been admitted for hypertension in 1998.			
	NeoRecormon (epoetin beta)	6000 IU, once a week sc		
	Etalpha (alfacalcidol)	0.25 microg twice daily po		
	Resonium A (polystyrene sulfonate)	15 g once daily po		
	Calci-chew (calcium carbonate)	500mg twice daily po		
	Folic acid	0.5mg once daily po		
	Fero-Gradumet (ferrous sulfate slow release)	105 mg once daily po		
	Seloken ZOC (metoprolol slow release)	200 mg once daily po		
	Enalapril	20 mg once daily po		
	prednisolone	7.5mg once daily po		
	Nexium (esomeprazole)	20 mg once daily po		

the reasons and causes for this, and their knowledge of the alert. Furthermore they were asked whether the study conditions resembled their normal daily working environment. Interviews were audio taped and transcribed verbatim.

Analysis

Type of handling was classified by analyzing observation forms, using the following definitions. Override = the order is confirmed despite the alert generated, irrespective of whether other measures are taken (e.g., an extra prescription for a gastro-protective drug). Annulment = the order is adjusted resulting in absence of the alert in the final order. Adjustment = the order is adjusted, but does not result in absence of the alert (e.g., lowering the dose in case of the DDI captopril-furosemide).

The expert panel consisting of 2 hospital pharmacists, 2 physicians and 1 medical informatics specialist defined correctness of handling and reasoning, and performance level using the SRK model. Correctness of handling and reasoning were assessed by consensus by a hospital pharmacist (HvdS) and internist (TvG). If the physician said he would monitor the serum level of glucose, potassium, the international normalized ratio (INR), or an electrocardiogram (ECG) and this was deemed appropriate, this was defined as correct handling, although these could

not be, and therefore were not, ordered during the test. Annulments of overdose alerts with the comment 'for later checking' were classified as 'correct', overdose overrides with the same comment as 'unable to classify', because less serious effects were expected from annulments than from overdoses. If the physician did not handle the alert completely during the test although this was possible (for example, did not add an extra prescription for gastric protection or restart hydrocortisone three days in advance), and also did not mention these extra measures, it was classified as incorrect. If the physician however mentioned these measures, but did not handle the task completely, the category was 'not able to classify'. Incorrect rules and reasoning were classified as 'incorrect rule', 'rule not applicable' (incorrectly applied), or, in the case of better alternatives, 'suboptimal reasoning' (failure to apply best rules).

A hospital pharmacist (HvdS) and medical informatics specialist (JA) categorized the performance level by consensus. Respondents who did not know why they performed a certain action, or admitted to not having noticed the alert were classified as SB, because SB behavior takes place without conscious attention or control and cannot be verbalized [2,10]. If justification of alert handling could be summarized as a rule of the type 'if-then' and the respondent did not seek advice elsewhere, this was classified as RB behavior. If the respondent made scenarios for the handling, was uncertain about the decision, sought clarification in the medical record, alert text or textbooks or commented that he/she would consult a specialist, it was interpreted as conscious cognitive behavior. This was classified as KB behavior, because the respondent then resorted to functional reasoning after easier responses with stored rules had failed. As more than one level of performance could be involved in carrying out a task, in case of doubt between cognitive levels, the higher cognitive level was chosen, in the same way as Hobbs [6].

Physicians following unknown alert recommendations without checking them were thought to be dependent on the drug safety alerting system. Those admitting to skipping alerts, feeling overwhelmed by large numbers of non-specific alerts, or commiting SB errors were said to be suffering from alert fatigue.

RESULTS

Ninety residents (33 from internal medicine, 57 from surgery) were invited for the study. Nineteen residents (21%) completed the test, 13 (39%) from internal medicine and 6 (11%) from surgery. One internal medicine resident had to be excluded because he misinterpreted the task to be performed in the study. He thought the order entry had to do with continuation of drugs the patient was already taking and he admitted to have overridden alerts for that reason. The 18 residents included were all in their 3rd to 6th year of residency and on average 33 years old.

Eighteen residents prescribing for these patient cases with 13 alerts should result in 234 alerts. However, only 204 alerts were generated of which 154 (75%) were overridden. Fifty alerts (25%) resulted in orders being annulled and/or adjusted. Thirteen alerts were not generated,

because the physician did not prescribe an interacting drug earlier in the test session (12 times) or unintentionally entered a lower dose (once). Seventeen alerts that were prevented intentionally, because the physician anticipated the alert, were included in the analysis of physicians' behavior.

Ten times (4.5%) correctness of handling could not be classified; the remaining 211 alerts were used for correctness analysis. Sixty-three alerts (30%) were categorized as handled incorrectly, because the action itself (51 times, 24%) and/or the reason for the handling were incorrect (34 times, 16%). RB errors were most abundant (40 errors, 63%), followed by KB (24%) and SB errors (13%). One physician showed SB behavior in 4 out of the 13 alerts. He admitted several times to having missed alerts because of speed of order entry, although he said the test environment resembled his normal work environment and time pressure did not have any effect.

Table 2 shows the number of physicians making errors in alert handling and error type. If physicians made more than one mistake in one alert, these are all mentioned. Error number and type varied enormously with alert type. The valproic acid overdose was mainly handled incorrectly because this antiepileptic drug is not well known to residents in internal medicine and surgery. Many physicians acted at the KB level and followed the alert recommendation for the maximum dose of valproic acid, which was too high for the indication neuropathic pain. Hydroxychloroquine was also unknown, but the recommendation in the overdose alert was correct and resulted in fewer KB errors.

It was surprising that for each alert many different rules were used for justifying handling. Although many respondents knew that the combination furosemide-captopril is a standard drug combination that may cause hypotension and affect potassium levels, the majority handled this DDI incorrectly and RB, probably because this DDI generally can be overridden justifiably. Overriding the time-dependent DDI digoxin-Antagel was often justified by rules that were incorrect or applied incorrectly. Some physicians thought these alerts regarding drug administration times should be handled by nurses, as was earlier proposed but not yet formalized [11], but other incorrect assumptions also played a role: 'drugs that are not absorbed do never interact' or 'digoxin serum levels rise upon addition of Antagel'. Half of the physicians said they would order an ECG after overriding the DDI tacrolimus-cotrimoxazole (although other studies showed ECGs are rarely recorded [12]). Other respondents thought ECGs were not necessary, QT prolongation was not serious, or cotrimoxazole used for *Pneumocystis carinii* prophylaxis could be stopped.

The high number of SB errors in the DDI alert paroxetine-diclofenac was remarkable, three physicians admitted not having noticed the alert, which appeared as a second DDI alert after prescribing diclofenac. A resident in surgery said: "I did not look through the new screen, and then I hit the button and suddenly it was gone, you do not get the warning again, and there is no button to get it back". The alert for the thousand-fold digoxin overdose was handled correctly and RB by all physicians and was even prevented by 15 of them.

Table 2 Numbers of respondents making errors in handling drug safety alerts and type of error
Alerts are shown in decreasing order of error numbers

Alert	Action correct		Errors				Mistakes (incorrect rules or reasoning)
	Yes	No	Total	SB	RB	KB	
DDI furosemide-captopril (0019)	3	15	15	0	13	2	Blood pressure is monitored and therefore *risk acceptable* (RB, IR) (5 times). Hypokalemia and *hypotension is no reason not to prescribe* this standard combination (RB, IR). *Hypotension is not likely* because these drugs are generally prescribed for hypertension (RB, IR) *An interaction does not always occur upon starting the drug* (RB, IR). *It is not my job to judge drug-drug interactions* (RB, IR). Diuresis, renal function and electrolytes (potassium) can be monitored (RB,KB, NA) (3 times). *Standard combination* recommended in cardiology guidelines (RB, NA) (2 times). An internist or cardiologist *initiated this combination long ago* (RB, NA).
OD valproic acid	5	11	11	0	3	8	High doses are *acceptable in neuropathic pain* (RB, IR). 900mg thrice daily *is acceptable* (KB, IR). Dose recommendation in alert text states that *600mg thrice daily is the maximum dose* (KB, NA) (5 times) Specialists have prescribed this, *I am not the person to adjust that* (RB,KB,SO) (4 times).
DDI digoxin-Antagel (0787)	7	8	8	2	5	1	Antagel is a relatively harmless drug, is not absorbed and *interactions therefore irrelevant* (RB, IR) (2 times). It is nurses' role *to tell patients* about administration times, and *they are informed about it* (RB, KB, IR) (2 times). The digoxin level is *rising* (RB, IR). I will *tell the patient* about taking it with an interval of 2 hours (RB, NA). Digoxin serum levels can be monitored and doses can be adjusted accordingly (RB, SO) (2 times).
DDI tacrolimus-cotrimoxazole (5088)	15	3	8	1	5	2	*ECG not necessary* because prophylaxis is more important than QT prolongation (RB, IR). *ECG not required* because symptoms of QT prolongation *can be observed on the ward* (RB, IR). *If a patient has never had QT problems, you may give this combination* (RB, IR). QT-interval prolongation alert *is no reason for stopping a medication order* (RB, IR). *Tacrolimus serum level* is influenced by many antibiotics, but can be monitored (RB, NA). *Switching* to an alternative antibiotic *is the easiest way* of handling this alert *(cotrimoxazole stopped)* (KB, IR). *Cotrimoxazole is less important* than tacrolimus *(cotrimoxazole stopped)* (KB, IR).
DDI paroxetine-diclofenac (3360)	9	4	5	3	2	0	*Gastric protection is not necessary for this patient* because diclofenac dose is low (RB, IR). *A lower paroxetine serum level* caused by diclofenac is not problematic (RB, IR).

Table 2 continued

Alert	Action correct		Errors				Mistakes (incorrect rules or reasoning)
	Yes	No	Total	SB	RB	KB	
DDI paroxetine-tramadol (4227)	11	5	5	1	3	1	*Increased sleepiness* due to the combination is not relevant (RB, IR). The patient has already been using this combination *for a long time without any problems*, so serotonin syndrome is not likely (RB, IR). Serotonin syndrome is *not life threatening* (RB, IR).
OD hydroxychloroquine	10	4	4	1	2	1	400mg twice daily is *often used in rheumatology* and the program generally uses too low overdose limits (RB, IR). This *overdose is not very serious*; someone has prescribed this for a certain reason (RB, IR). Exacerbation is probably very serious; *dose is acceptable for short-term use* (KB, IR).
DDI carvedilol-diclofenac (0272)	14	1	4	0	4	0	The issue (for surgical residents) is whether the patients get their drugs before and after surgery in the way they have been prescribed or they have already used them for years. We do not think about whether it is a DDI or should be handled by us, that is not the issue (RB, IR) You may give diclofenac to people using an *ACE inhibitor* (RB, NA). Diuresis, renal function and electrolytes can be monitored (RB, NA).
DDI acenocoumarol-cotrimoxazole (0590)	17	0	1	0	1	0	I will monitor the *PTT* (RB, IR)
DDI insulin aspart-bisoprolol (0302)	18	0	1	0	1	0	*It is OK because another physician has decided this to be correct in the past* (RB, SO).
DO tacrolimus-mycophenolate mofetil	18	0	1	0	1	0	*Tacrolimus serum level* is monitored and dose adjusted accordingly (RB, NA).
DO hydrocortisone–methylprednisolone	15	0	0	0	0	0	-
OD digoxin	18	0	0	0	0	0	-
Total	160	51	63	8	40	15	

RB = rule based KB = knowledge based SB = skill based
IR = incorrect rule or reasoning NA = rule not applicable SO = suboptimal rule or reasoning
ECG = electrocardiogram PTT = prothrombin time
Wrong parts are shown in *italics*. Numbers between brackets refer to DDI code in the Dutch drug database.

There was no difference between the two specialties if only correctness of the actions of overriding or annulment were taken into account (76% for both internal medicine and surgery). But residents in surgery made RB errors twice as often as residents in internal medicine and overrode or annulled alerts correctly by using wrong rules, or by rules not applicable to the situation in 13% of cases (internal medicine 5%).

Three of the five respondents who followed the incorrect dose recommendation for valproic acid commented they would check it later with a specialist or textbook, whereas two of them did not mention any additional checks, and were probably dependent on alert information provided by the system. Six residents followed the correct dose recommendation of hydroxychloroquine

200mg twice daily. Three of them commented they would consult a rheumatologist afterwards, one planned to refer to a textbook and two did not mention additional checking.

Five residents (28%) were judged to have suffered from alert fatigue because of their comments shown in Table 3. Besides that, another physician committed 3 SB errors. Furthermore, residents referred to other aspects that could further add to alert fatigue: too low dose limits, DDIs that should be suppressed because of low incidence of adverse events, and the necessity for scrolling down the whole alert text to find the conclusion. One resident on the other hand emphasized drug safety alerting as a positive feature of the CPOE.

The respondents judged the test environment to be comparable with, or quieter than, their normal work environment. The respondents said the observer had little (3, 17%) or no influence (15, 83%) on their behavior, and 9 physicians (50%) said they did not notice the observations. Eleven respondents did not experience any effect of time pressure, 2 a small effect, and 3 physicians said they would have checked a textbook if they had had more time available. Two respondents said that generally they have more patient information available than they did in the test.

Table 3 Remarks made suggesting alert fatigue

There are so many drug-drug interactions that are irrelevant, that I am often inclined to rapidly click them away [resident in internal medicine].
Those alerts, there are so many, they should be as limited as possible [resident in internal medicine].
You are completely overwhelmed by those (QT) alerts, so you are not setting your heart on it anymore [resident in internal medicine].
You get these overdose alerts really in and out of season [resident in surgery].
All those drug-drug interactions and all those things you get reported drive you mad. You get all those DDIs reported; you simply skip them. I only cancel orders in case of overdose alerts. If I have to consider every DDI, than I am busy with it, all day, and that is not my job. We do not think about whether it is a DDI or should be handled by us, that is not the issue [resident in surgery].

DISCUSSION

Errors in alert handling

This study in a simulated work environment showed that physicians handled many drug safety alerts incorrectly at the RB level, using many different rules. Respondents often justified their overrides referring to monitoring serum levels or patient conditions, but the substances mentioned or patient parameters were often incorrect. Four respondents said they would monitor renal function, diuresis or electrolytes when blood pressure monitoring was appropriate, others referred to tacrolimus serum level monitoring or clinical observation when ECG recording was indicated. In several CPOEs the override reason 'patient being monitored' can be selected from a dropdown box and pharmacists perceive this as useful for order verification [13-15]. Our findings suggest the reason 'patient being monitored' is insufficient to prevent error and should

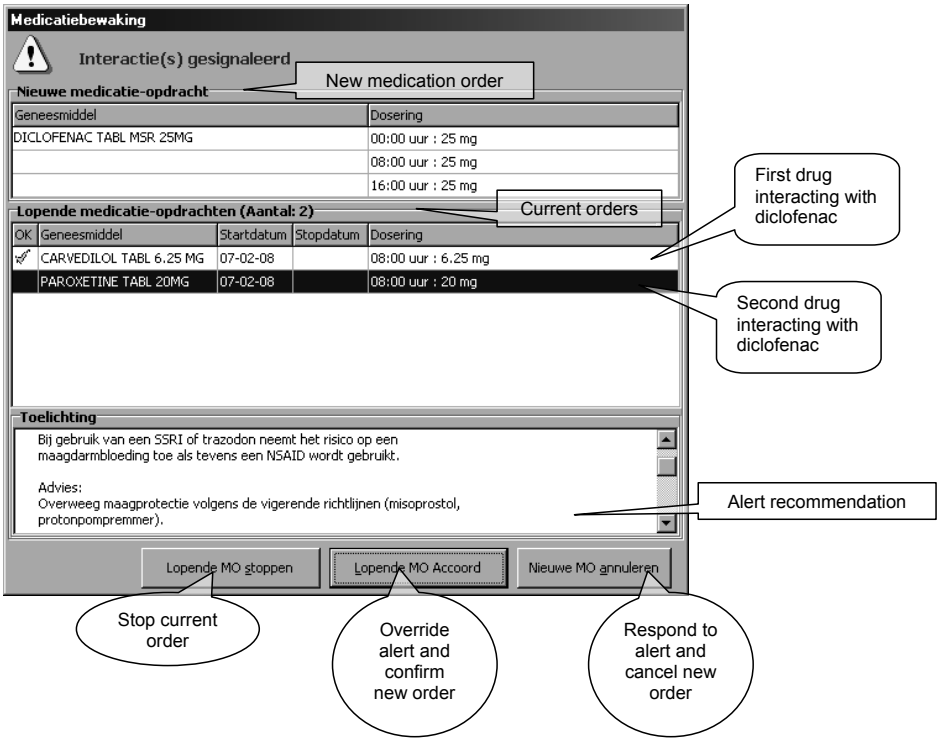

Figure 1 Drug-drug interaction alert
Example of alert screen presented to a physician ordering diclofenac (new order) when carvedilol and paroxetine (current orders) are already on the patient's medication list. After overriding the first DDI carvedilol-diclofenac, a √ is placed before carvedilol and the alert text for paroxetine-diclofenac is presented in the same place as the former alert recommendation.

ideally be accompanied by clinical rules checking for correct serum levels, ECG recordings, and blood pressure measurements.

The high number of SB errors in handling the combination paroxetin-diclofenac can probably be attributed to the presentation of two DDI alerts in one pop-up screen (Figure 1), as was mentioned by one of the physicians. Separate screens pop up for different alert types (i.e., overdoses, duplicate orders and DDIs) and generally only one alert is presented per screen. In the case of diclofenac generating two DDI alerts, the physician may overlook the second alert, thinking that the override button for the (first) alert has not worked properly, and thereby unintentionally override the second alert. Usability studies are necessary to find out whether double alert presentation indeed provokes unintended overrides and whether a different method of presentation can prevent them.

SB errors were observed less frequently than RB and KB errors, which is in line with the literature [6]. Generally SB behavior is frequently used, with a low error rate [6]. In this study, however, only 5% of cases were categorized as SB and the observed SB error rate was very high (80%). At first sight, these findings seem to deviate from normal alert handling, but it can be

questioned whether drug safety alerts can be performed adequately on a SB level. The alert has to be read and understood before the alert can be handled appropriately, and this requires RB or KB behavior. The SRK framework is generally used for error analysis in industrial environments, where easily interpretable displays result in SB behavior. In this study, only overdose alerts are presented graphically with bars in red and green which are easily interpretable. All DDI and duplicate order alerts appear similar at first sight and it is necessary to read the drugs involved and/or the alert text. This would imply that SB behavior should be absent in alert handling for DDIs and duplicate orders and explains why a high error rate is observed if these alerts are handled at the SB level.

The percentage correctly handled drug safety alerts was 76% for both specialties, but this number only included correct overriding, adjustment or annulment, and did not include correct monitoring, rules, or reasoning. The rules surgical residents used to justify their handling were incorrect twice as often as the rules used by residents in internal medicine. These mistakes, accidentally resulting in correct handling in these simulated patient cases, could easily provoke incorrect handling and patient harm in other situations with the same alerts. Generally surgeons are less pharmacotherapy-minded than internists and therefore we expected less drug-related knowledge, more KB and less RB behavior. The percentages RB and KB behavior were comparable however (RB 71% and 70%; KB 26% and 25%), which suggests that both groups were about equally certain about their answers.

Signs of alert fatigue or dependency

Alert fatigue was clearly present for several respondents from both specialties, but was absent in some physicians who were satisfied with the alerting function of the CPOE. Dependency on alert generation and alert recommendations could not be proven as none of the respondents admitted to relying fully on the alerting system. Those using the alert recommendations either intended to perform additional checks or did not mention whether they would check.

Error management

Error management aims at prevention, visible error notification, and mitigation of the effects of errors [16,17]. Errors committed on different cognitive levels require different interventions to prevent them [4,6]. KB behavior generally is very error prone and this type of behavior should be prevented and be replaced by RB behavior as much as possible. As drug treatment is very complex, prevention of KB behavior is impossible, although rules about how to handle unknown alerts might be helpful (e.g., read the alert text completely and carefully). Informative, clear alert texts might help physicians in KB decision making and would probably lower the error rate.

Rules used in RB behavior have been learned from textbooks, other persons or from previous experience and may be very strong if employed successfully in the past. RB errors are categorized as incorrect rules, incorrectly applied rules, and failures to apply best rules and may be

due to insufficient training. Education is proposed as a measure to counteract RB errors, but is time consuming [4].

Generally, SB errors are easily detected because the intended plan is correct, but in this study this was not the case. The SB 'unintended override' errors were almost invisible in Medicatie/EVS® version 2.30 ('you do not get the warning again, and there is no button to get it back') and therefore feedback about the erroneous action was absent. In a newer version of this CPOE (2.40), an override icon is present in the medication overview, which can be opened to view the drug(s) involved, and the complete alert text. This new feature improves error notification by prescribers and supervisors and might play a role in error reduction. It furthermore enables dedicated alert handling at a more suitable time, which seems to be useful as lack of time has been shown to be an important factor negatively affecting decision support acceptance [18].

Reason's model of accident causation applied to drug safety alerts in CPOE shows that active failures, such as ignoring and misinterpreting alerts and wrong selections, should be prevented by reducing or removing error-producing and latent conditions [1].

Ignoring

Several respondents admitted to clicking alerts away without reading them and one respondent could not recall handling of 4 different alerts. Suggested measures to prevent alerts from being ignored are improving specificity and directing time-dependent DDI alerts to other people in the workflow (nurses). Implementation of the sequence indications available in the Dutch drug database would improve specificity by reducing the high number of false-positive sequence-dependent DDIs (furosemide-captopril) [7].

Misinterpretation

Misinterpretation was rife, as shown by the high numbers of wrong or inapplicable rules and reasoning. Misinterpretation may be due to unclear alert texts or texts that are not read completely. The interviews performed in this study suggest that both play a role. The recommended response to the alert, which is generally located low down in the alert text, was rarely mentioned in the handling justifications. Respondents often referred to drug serum levels that were inappropriate for the alert at hand, but which may have been useful in other alerts. The drug name itself probably already triggered rules before alerts were read properly. Length, content, and sequence of the alert texts provided by the Dutch national database have been mentioned negatively in another study as well [7]. Unambiguous, concise and easy-to-understand alerts, with easily accessible background information would add to usefulness of the alerts [1,7,19-22]. Insufficient training also appeared to play a role. Several respondents did not know that serotonin syndrome is a serious adverse event, and did not recognize the sequence of ordering captopril or furosemide as an important risk factor. Training is proposed as an important remedy to reduce misinterpretation. Concise alert texts may add to better understanding by provid-

ing informal training in the limited time during order entry, but easily accessible additional information is mentioned as an important factor for useful alerts also [19-21].

Wrong selection

A few times respondents made a wrong selection, because they trusted the alerting system (and followed the incorrect dose recommendation for an unfamiliar drug), because the alert presentation was unclear (two DDI alerts in one screen provoking oversight) or because the frequently-overridden DDI was generally irrelevant (DDI captopril-furosemide). By similarity matching and frequency gambling this resulted in the very strong rule that this latter DDI was irrelevant and did not require any specific action besides blood pressure monitoring. The introduction of sequence indications is proposed to improve specificity and prevent this type of error, but this should be accompanied by adequate information and monitoring because it is difficult to change RB behavior based on such a strong rule.

Latent conditions

Besides insufficient training, other latent conditions that may have caused errors in handling drug safety alerts were dependency on the alerting system and trust in checks by other people [1]. Dependency on the alerting system could not be proven in this study. One resident mentioned that judging drug safety alerts was not a surgeon's job, thereby relying on other people. These comments suggest that responsibility for alert handling is probably not clearly and sufficiently communicated to the users.

Strengths and weaknesses of the study

The study design combining disguised observation and interviews directly afterwards enabled us to gain an insight into different types of alert handling, including SB behavior, that cannot be evaluated with the uncombined methods. The interviews revealed useful and very relevant safety information that would have remained hidden by analysis of override reasons from dropdown boxes. Less familiar alerts could be studied in a relatively small time frame, whereas disguised observation is time consuming and only reveals information on the emerging (mainly known) alerts. The closing questions on study validity revealed that the study resembled the normal work environment to a great extent.

This study was performed in one hospital, with one CPOE and only 18 physicians who were willing to participate, resulting in selection bias. However the great variety in handling and reasoning suggests that inclusion of other respondents would probably not result in different findings. It appeared to be very difficult to recruit residents, especially the younger ones and those from surgery, because the first years of residency take mainly place outside the academic hospital, and residents in surgery were not very interested in drug prescribing. Therefore, the effect of level of training on performance could not be studied. A drawback of the study design was that it was impossible to check whether the proposed monitoring of serum levels or

patient parameters would be performed in reality. Nine residents (50%) said they would check the QT interval on the ECG, but in general practice ECGs are rarely made when QT alerts are overridden [12]. The percentage of correct monitoring could therefore be lower than stated by the respondents. Furthermore, surgical residents said they would never initiate beta-blockers or ACE inhibitors themselves, but they were asked to prescribe them during the study. Incorrect handling, rules or reasoning for newly prescribed drugs could therefore be less than during the study.

It can be questioned whether classification of behavior according to the SRK model was always completely correct. During observation, KB behavior was easily detected, because the decision took a relatively long time, scenarios were muttered, or information sources were consulted. Based on observation only, the choice between SB and RB behavior appeared to be very difficult however. We used the interviews to assign categorization of cognitive levels, which might have resulted in incorrect *post hoc* categorizations. The actions for which clear reasons were given in the interviews were categorized as RB, although these could have been performed on a SB level and reasons constructed afterwards. On the other hand, sometimes people cannot remember why they acted in a certain way, even if the time interval between the action and the interview is short. In our study this could have resulted in SB categorization in the case of actions performed at a RB level. Furthermore, a person's task performance may involve more than one cognitive level at once and the cognitive control varies along a continuum, making classification difficult sometimes [6]. In case of doubt, we followed Hobbs in consistently choosing the higher performance level [6].

It can further be questioned whether the SRK model is adequate for obtaining an insight into how cognitive processes play a role in (erroneous) alert handling. The SRK model is a basic model in cognitive psychology describing information processing and is widely used to identify error types, which may range from strong habits, used unconsciously, to cognitive overload at the conscious level. It provides a common terminology for human factors studies and is one of the few tools that can be used to describe the interaction between a person and a task in terms of the cognitive demands of the task [6]. Although cognitive load theory also involves information processing, this theory mainly focuses on learning and instruction in complex cognitive domains, which was not the focus of this study [23].

The main goal of this study was not to correctly categorize all performance levels, but to gain an insight into alert handling and corresponding errors impairing patient safety as a starting point for future studies on improvement of drug safety alerting. We therefore developed a study simulating the normal work environment, instead of designing a laboratory study perfectly able to categorize performance levels but not resembling daily life.

CONCLUSIONS

Drug safety alerts were mainly handled rule based, but incorrect rules or reasoning were often used to justify actions. Residents in surgery justified their actions incorrectly twice as often as residents in internal medicine. Main causes of errors were rules that were incorrect or not applicable, such as monitoring of incorrect serum levels or patient parameters, among others. Insufficient training and low specificity played a role in erroneous alert handling. Furthermore, a second alert in one pop-up screen was often overlooked. Roughly a quarter of residents showed signs of alert fatigue.

Future research should include usability studies to investigate how alerts should be presented to be safe and acceptable to clinicians (several alerts in one pop-up, clear and concise alert texts, nonintrusive alerts).

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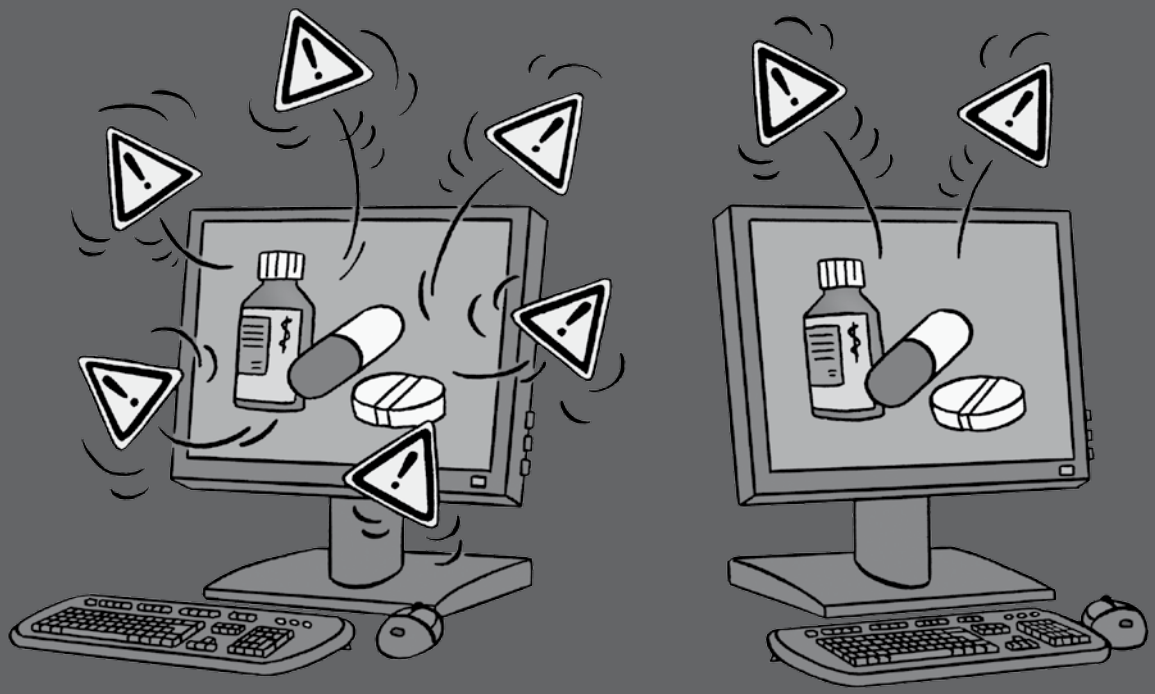
Chapter 2.4

Functionality of drug safety alerting in computerized physician order entry systems



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ABSTRACT

Purpose: To evaluate the functionality of drug safety alerting in hospital computerized physician order entry (CPOE) systems by a newly developed comprehensive test.

Methods: Comparative evaluation of drug safety alerting quality in 6 different CPOEs used in Dutch hospitals, by means of 29 test items for sensitivity and 19 for specificity in offices of CPOE system vendors. Sensitivity and specificity were calculated for the complete test, and for the categories 'within-order checks', 'patient-specific checks', and 'checks related to laboratory data and new patient conditions'. Qualitative interviews with 16 hospital pharmacists evaluating missing functionality and corresponding pharmacy checks.

Results: Sensitivity ranged from 0.38 to 0.79 and specificity from 0.11 to 0.84. The systems achieved the same ranking for sensitivity as for specificity. Within-order checks and patient-specific checks were present in all systems, alert generation or suppression due to laboratory data and new patient conditions was largely absent. Hospital pharmacists unanimously rated checks on contraindications (absent in 2 CPOEs) and dose regimens less than once a day (absent in 4 CPOEs) as important. Pharmacists' opinions were more divergent for other test items. A variety of pharmacy checks were used, and clinical rules developed, to address missing functionality.

Conclusions : Our test revealed widely varying functionality and appeared to be highly discriminative. Basic clinical decision support was partly absent in two CPOEs. Hospital pharmacists did not rate all test items as important and tried to accommodate the lacking functionality by performing additional checks and developing clinical rules.

INTRODUCTION

Computerized physician order entry (CPOE) systems have been shown to reduce medical errors considerably [1-6], although error-producing conditions in the software, such as low specificity and low sensitivity, may compromise patient safety [7]. Low sensitivity (poor ability to generate alerts in potentially dangerous situations) may result in medication errors because of an absence of alerts. Low specificity (inability to prevent irrelevant alerts) may result in a deluge of alerts and subsequently alert fatigue (important alerts being ignored along with clinically unimportant ones) [7,8]. So, we are faced with a confusing and conflicting situation: increasing sensitivity may result in an increased percentage of inappropriate alerts, which decreases specificity [7].

The performance of drug safety alerting systems depends on the information content of the knowledge base, alerting features (functionality) and local configuration and customization [7]. Performance deficits therefore may have different causes. Studies on the performance of alerting systems in CPOE mainly focus on one type of drug safety alerting or on the content of the knowledge base [9-13] and more comprehensive tests are not always publicly available [14].

The aim of this study was to develop a comprehensive test to measure functionality, to evaluate functionality within hospital CPOEs, and to evaluate how missing functionality is rated and compensated for by pharmacy measures. Performance deficits in this test directly point at software deficiencies, because the influence of knowledge base, configuration and customization are eliminated. The questions posed by this study are:

1. What is the functionality of drug safety alerting in Dutch hospital CPOEs?
2. What measures are taken to prevent errors due to lacking functionality?

BACKGROUND

The Dutch national drug database (G-standard) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP), contains safety information about all licensed drugs in the Netherlands with respect to dosing, duplicate orders (DO), drug-drug interactions (DDIs), allergies, contraindications (CIs), pregnancy, renal function, and pharmacogenetics [15]. DDIs and CIs are categorized depending on 1) their influence on drug effect (yes or no) and 2) the need for appropriate action (yes or no). As a result the following three permutations of DDIs and CIs exist: yes/yes, yes/no and no/no. The same permutations exist for drug excretion affected by renal function or by pharmacogenetic profiles [15]. The G-standard contains sequence indications for alerts that are only relevant when new drug A is added to an existing regimen including drug B and not the other way round [16]. If a paediatric dose is unknown, the G-standard indicates whether the percentage of the adult dose can be read off from the Denekamp scale with the patient parameters age and/or weight [17]. All Dutch CPOEs make use of the G-standard, which

is updated monthly [18-23]. Hospitals can customize alerting by adjusting database information, for example by changing a maximum dose level, or by configurating functionality of the CPOE, for example turning off all yes/no DDI alerts.

METHODS

Test development

Five drug safety alert categories with different variables were defined: dose, DDIs, CIs, duplicate order, and a rest group (other). The categories and some examples of variables are presented in Table 1. Variables requiring different functionalities were selected from the Dutch national drug database, from the literature, and from our own experience [15,24,25].

Table 1 Categorization of testitems

Category	Variables
Dose	Overdose
	Overdose/kg bodyweight
Drug-drug interactions (DDIs)	Sequence-dependent DDI
	Time-dependent DDI
Contraindications (CI)	Penicillin allergy
	Pregnancy
Duplicate order (DO)	Identical drugs
	Comparable drugs
Other	Renal function (bad renal function)
	Pharmacogenetics (poor metabolizer)

Variables were allocated to the sensitivity and/or specificity test as test items. In the sensitivity test alerts should be generated, in the specificity test alert generation should be absent. Forty different test items for drug safety alerting were discerned in the Dutch national drug database (23 for sensitivity and 17 for specificity) and included in the tests. An additional 8 test items, based on the literature and own experience were also included. Three patient cases were developed per test item. A patient case consisted of 1 or 2 prescriptions for a patient with known age, body weight and height, and when necessary for the test item, indication, contraindication, renal function, pharmacogenetic profile or serum level. Patient cases per testitem varied widely with respect to drug, route, and alert code. Five different patient profiles were used for the test, with differences in gender, age and body weight. Definition of cases was not guided by the number of alerts usually generated, the seriousness of the alert or the costs involved, but only by functionality requirements. Test items were categorized as within-order checks, patient-specific checks, and checks related to laboratory data and new patient conditions [26]. The functionality test was checked for completeness and correctness with the latest

version of the Dutch drug database at the KNMP office in November 2006 and is presented in the appendix to this chapter.

Functionality evaluation

CPOEs with at least two sites of implementation were selected from the Dutch Association of Hospital Pharmacists' (NVZA) private website [27]. System vendors were included that gave informed consent for testing including the intention to publish the results. The test took place in the offices of system vendors, to prevent influence of local configuration, and was performed in January 2007 using a version already available on the market and/or in use by one or more hospitals. If two cases of the test item showed negative results, a third case was entered and the software vendors were asked if the results were as expected. Software vendors were allowed to change configuration (turn functionality on or off) in case of unexpected negative results, but then all three cases of the test item had to be entered again and show similar results (i.e., alert absence or presence). Test results were discussed with the software vendors directly after finishing the test. Sensitivity and specificity per system were calculated for all test items together, and for the different categories ('within-order checks', 'patient-specific checks', and 'checks related to laboratory data and new patient data').

Evaluation of missing functionality

Hospital pharmacists known to be actively involved in local CPOE implementation were individually asked about the perceived importance of missing functionality in their CPOE and measures to address it. Interview results were typed out and checked for correctness and completeness by respondents.

RESULTS

In January 2007, 8 different CPOE systems had been introduced into Dutch hospitals. Six CPOEs, represented by 4 companies, were used in more than one hospital and selected for inclusion. All software vendors gave informed consent for testing and the intention to publish test results. Eighty-nine percent of all Dutch hospitals with a CPOE (41/46) used one of these six systems.

Order entry of the whole test set lasted between 2.25 and 5.5 hours per CPOE. Four CPOEs generated pop-up alerts whereas two systems (Theriak and TPM, now called Pharma (VCD Automatisering) [21-23]) showed the alerts nonintrusively. A configuration change was necessary in three cases, once turning on checking on Denekamp scale for paediatric dosing, two times turning off yes/no alerts. For all test items, test results in patient cases a, b, and possibly c were similar.

An overview of the functionality of the software systems is shown in Table 2. Sensitivity ranged from 0.38 to 0.79 (38 to 79% of the alerts were correctly generated), and specificity

Table 2 Overview of drug safety alerting functionality of Dutch hospital CPOE systems
CPOEs are presented in descending order of overall specificity

CPOE tested (version)	Overall		Within-order		Patient-specific		New data	
	sens (n=29)	spec (n=19)	sens (n=14)	spec (n=6)	sens (n=13)	spec (n=10)	sens (n=2)	spec (n=3)
TPM* (2.8.2)	0.79 (0.83$^{\$}$)	0.84	0.79	0.83	0.92	0.90	0	0.67
Zamicom (2006-1)	0.66	0.68	0.79	0.67	0.62	0.70	0	0.67
Chipsoft (4.8 FP)	0.66 (0.69$^{\$}$)	0.53	0.79	0.50	0.62	0.50	0	0.67
Centrasys (1.20 SP1)	0.48	0.47	0.43	0.50	0.62	0.40	0	0.67
Medicatie/EVS (2.41)	0.48	0.21	0.57	0.16	0.46	0.30	0	0
Theriak (3.4.3)	0.38	0.11	0.50	0.33	0.31	0.00	0	0

sens = sensitivity, spec =specificity, n =number of test items

* Now called Pharma (VCD Automatisering)

$ Functionality for sequence-dependent DDIs could not be shown during the test, but was said to be present. If this functionality was indeed present, this resulted in the figures shown between brackets.

from 0.11 to 0.84 (11 to 84% of the alerts were correctly suppressed). The systems achieved the same ranking for sensitivity as for specificity. Many within-order and patient-specific checks were present, whereas few systems used measured serum levels and emerging patient data for alert generation or suppression.

The results of the sensitivity and specificity tests are presented in Tables 3 and 4. In the sensitivity tests the number of test items present ranged from 11 to 23. None of the CPOEs detected all potential safety problems, and alerting on contraindications (categorized as basic clinical decision support [28]) was absent in 2 systems. The CPOEs did not generate alerts for 2 to 16 out of the 19 test items in the specificity test.

All software house representatives agreed with the outcome of the test for their CPOE, except for the sub-variable 'yes/yes DDI sequence' in the sensitivity test of the Chipsoft and TPM systems [19,22]. Software vendors and hospital pharmacists using these CPOEs said this functionality was present, but this could not be shown during the test.

For each of 5 CPOEs 3 hospital pharmacists could be recruited for an interview about missing functionality. For Theriak that appeared to be used in only one hospital, one pharmacist was interviewed. Hospital pharmacists differed in their estimate of the importance of several test items and used different measures to prevent errors due to lacking functionality. They perceived alerts on 'frequency less than once a day incorrect', which were absent in 4 out of 6 systems, to be very important, specially for methotrexate, and performed a variety of pharmacy checks to compensate for this. [Methotrexate once daily results in serious adverse events, even in low doses of less than 20mg. Methotrexate should be dosed once a week or at most thrice weekly. Frequencies of less than once a day could not be adequately checked in 4 out of 6 CPOEs tested.]

Several functionalities were not missed, because of the limited number of drugs involved ('indication-dependent overdose', 'contra-indication gender'), prevention by other alerts or

Table 3 Results of sensitivity test

Category	Test item	Example of case	TPM*	Klinicom	Chipsoft	Centrasys	Medicatie/EVS	Theriak
Dose	Overdose (absolute)[1]	Levothyroxine 275 microg per os once daily (adult) (max = 250 microg)	+	+	+	+	+	+
	Overdose combination product[1E]	Co-amoxiclav 1500/375 mg/mg per os thrice daily (adult) (max = 1750/250 mg/mg daily)	+	+	+	+	+	+
	Frequency per day incorrect[1]	Paracetamol 500mg per os eight times a day (max = 6 times)	+	+	+	-	-	-
	Frequency less than once a day incorrect[1]	Methotrexate 7.5mg per os once daily (max = thrice weekly)	+	-	+	-	-	-
	Underdose[1E]	Amoxicillin 375 mg per os twice daily (adult) (min = 500 mg twice daily)	+	+	+	-	+	-
	Overdose due to duplicate order[1E]	Diclofenac 50 mg per os thrice daily + diclofenac 100 mg rectally twice daily (max = 200mg)	+	-	-	-	-	-
	Overdose per kg body weight[2]	Morphine 10 mg/kg (330 mg) per os once daily (child 9 years old) (max= 10 mg)	+	+	+	+	+	+
	Overdose per m^2 body surface area[2]	Aciclovir 1000 mg/m^2 iv thrice daily (child 1.12m^2) (max = 500 mg/m^2 thrice daily)	+	+	+	+	+	+
	Weight limit for drug dose[2]	Azithromycin 500 mg per os twice daily (child 4kg) (<45 kg dose = 10 mg/kg)	-	-	-	-	+	-
	Dose calculated with help of Denekamp scale[2]	Frusemide 60 mg per os once daily (child 9 years old, 33 kg, 138cm)	+	-	+	+	-	+
	Dose calculation with help of Denekamp scale not allowed[2]	Frusemide 60 mg per os once daily (child one month old, 4kg, 60 cm) (Denekamp scale not allowed for children < 6 months)	+	-	-	-	-	-
	Indication-dependent overdose[2]	Metoprolol 200 mg per os once daily (indication = decompensatio cordis)	+	-	-	-	+	-
DO	Irrational duplicate order[1]	Bumetanide per os and iv	+	+	+	+	+	+
	Irrational pseudo-duplicate order [1]	Simvastatin and atorvastatin	+	+	+	+	+	+

Table 3 continued

Category	Test item	Example of case	TPM*	Klinicom	Chipsoft	Centrasys	Medicatie/EVS	Theriak
DDI	Yes/yes drug-drug interaction[1]	Tramadol and fluoxetine	+	+	+	+	+	+
	Yes/yes sequence-dependent DDI[1]	Bumetanide and ramipril	-[$]	+	+	-[$]	+	+
	DDI due to stopping medication[1]	Phenytoin and fluoxetine. Fluoxetine is stopped (serum level phenytoin decreases).	-	+	-	-	-	-
	Period after stopping medication[1]	Tranylcypromine starts directly after stopping fluoxetine (5-week interval needed).	+	+	-	-	-	-
	Incorrect time interval[1]	Algeldrate/magnesium hydroxide and ciprofloxacin at the same time (4-hour interval needed)	+	+	+	+	+	+
CI	Yes/yes contraindication[2]	Propranolol 80 mg per os once daily (CI = asthma)	+	+	+	+	-	-
	Allergy[2]	Amoxicillin 500 mg per os once daily (CI = penicillin allergy)	+	+	+	+	-	+
	Pregnancy[2]	Isotretinoin 40 mg per os once daily (CI = pregnancy)	+	+	+	+	-	-
	Gender[2]	Testosterone 80 mg twice daily (CI = woman)	+	-	+	-	+	-
	Age[2]	Loperamide 2mg once daily (child one year old) (CI < 2 years)	+	+	-	+	+	-
Other	Wrong route[1E]	Diclofenac tablet 50mg iv once daily	-	-	+	-	-	-
	Yes/yes renal function[2]	Metformin 500 mg per os thrice daily (adult, GFR= 15 ml/min) (CI GFR < 10-30 ml/min)	+	+	+	+	-	-
	Yes/yes pharmacogenetics[2]	Clomipramine 75 mg per os once daily (adult, poor metabolizer CYP2D6)	+	+	-	-	-	-
	Serum level not measured[3E]	Lithium carbonate 400 mg per os once daily (serum level Li not measured)	-	-	-	-	-	-
	Serum level too high/too low[3E]	Lithium carbonate 400 mg per os once daily (serum level Li= 3 mmol/l, too high) (normal serum level 0.6-1.2 mmol/l)	-	-	-	-	-	-

+ = alert has been generated; - = alert has not been generated; DO = duplicate order; DDI = drug-drug interaction; CI = contraindication; GFR = glomerular filtration rate; 1 = Within-order check; 2 = Patient-specific check; 3 = Check after changing patient data; E = extra functionality, not dependent on Dutch drug database; $ vendors and hospital pharmacists said this functionality was available, but it could not be demonstrated during the test.

* Now called Pharma (VCD Automatisering)

Table 4 Results of specificity test

Category	Test item	Example of case	TPM*	Klinicom	Chipsoft	Centrasys	Medicatie /EVS	Theriak
Dose	Weight limit[2]	Azithromycin 500 mg per os twice daily (child 80 kg) (>45 kg 500 mg twice daily)	-	-	-	-	+	-
	Indication-dependent dose[2]	Metoprolol 200 mg per os once daily (indication = angina pectoris)	+	-	-	-	+	-
DDI	No/no DDI[1]	Acetylsalicylic acid and clopidogrel	+	+	+	+	+	-
	Yes/no DDI[1]	Digoxin and frusemide	+	+	+	-	-	-
	No/no sequence-dependent DDI[1]	Bumetanide and ramipril	+	+	-	+	-	-
	Correct time-interval[1E]	Algeldrate and ciprofloxacin with 6 hour time interval (time interval of 4 hours needed)	-	-	-	-	-	-
DO	Duplicate order systemic-local (irrelevant)[1]	Hydrocortisone tablet 20 mg per os and hydrocortisone cream 2% cutaneously	+	+	+	+	-	+
	Pseudo-duplicate order rational[1]	Soluble insulin (Actrapid) sc and insulin detemir sc	+	-	-	-	-	+
CI	No/no CI[2]	Betahistine 8mg per os thrice daily (CI= asthma)	+	+	+	+	-	-
	Gender correct[2]	Testosterone 50 mg per os once daily (man)	+	-	+	-	+	-
	Yes/yes CI absent [3]	Propranolol 80 mg per os once daily (CI asthma removed)	+	+	+	+	-	-
	Pregnancy absent[3]	Isotretinoin 40 mg per os once daily (CI pregnancy removed)	+	+	+	+	-	-
Other	No/no renal function[2]	Doxycycline 100 mg per os once daily (adult, GFR = 20 ml/min)	+	+	+	+	-	-
	Yes/no renal function[2]	Tolbutamide 500 mg per os once daily (adult, GFR = 20 ml/min)	+	+	+	+	-	-
	Normal renal function[2]	Metformin 500 mg per os thrice daily (adult, GFR = 75 ml/min) (dose adjustment needed if GFR < 50 ml/min)	+	+	+	+	-	-
	No/no pharmacogenetics[2]	Clozapine 25 mg per os once daily (adult, intermediate metabolizer CYP2D6)	+	+	-	-	-	-
	Yes/no pharmacogenetics[2]	Paroxetine 20 mg per os once daily (adult, intermediate metabolizer CYP2D6)	+	+	-	-	-	-
	Normal pharmacogenetics[2]	Clomipramine 75 mg per os once daily (adult, normal metabolizer CYP2D6)	+	+	-	-	-	-
	Serum level measured and within limits[3E]	Lithium carbonate 400 mg per os once daily (serum level Li = 1 mmol/l, normal)	-	-	-	-	-	-

+ = alert has not been generated; - = alert has been generated; 1 = Within-order check; 2 = Patient-specific check; 3 = Check after changing patient data; E = extra functionality, not dependent on Dutch drug database; DO = duplicate order; DDI = drug-drug interaction; CI = contra-indication; GFR = glomerular filtration rate

* Now called Pharma (VCD Automatisering)

measures (alerts for 'overdose' or 'underdose' instead of alerts for 'frequency per day incorrect', therapeutic drug monitoring instead of alerts for 'yes/yes pharmacogenetics'), new problems arising (indication-dependent dose checking based on diagnosis codes used in ambulatory care, which deviate from the hospital diagnosis codes), unavailability of genotyping ('yes/yes pharmacogenetics'), or because pharmacokinetic and pharmacodynamic differences between children and adults are not taken into account ('dose calculation with help of Denekamp scale') [29]. Comments on testitems and measures taken are summarized in Table 5.

DISCUSSION

Despite a common knowledge base, the functionality of drug safety alerting in the CPOEs varied widely and the tests performed appeared to be highly discriminative. It was expected that improvement in sensitivity would result in less specific alerts, but this study showed the contrary with the same CPOE ranking for sensitivity and specificity. It appeared that the vendors of the best-performing CPOEs tried to develop new functionality as soon as the safety information became available while other CPOE vendors awaited requests for new functionality from health care providers.

TPM [23] was the best CPOE choice with respect to drug safety alerting, with the highest sensitivity and specificity, and with alerts on CIs and once-daily methotrexate dosing. However, this CPOE system presents drug safety alerts nonintrusively and it is not known whether this kind of presentation results in effective prevention of adverse events [16].

The hospital pharmacists differed in their rating for absent functionality and in the pharmacy checks they performed to compensate for it. However, several measures could be questioned from a safety perspective, e.g., visually checking whether a period of several weeks after stopping a drug is taken into account, checking renal function only when serum drug levels are being ordered, checking serum levels only when DDI alerts are overridden. Checks based on serum levels or performed in existing orders after changing patient conditions were mainly absent, but many hospital pharmacists thought development of clinical rules could compensate for this.

Strengths and weaknesses

This test was newly developed and used for evaluation of hospital CPOEs. To ensure reliability and objectivity of the test, several measures were taken. All patient cases were tested with the latest version of the G-standard at the KNMP office, two patient cases per test item were entered and if unexpected results were obtained or configuration changed, all three cases were entered and had to show similar results. Prescriptions were cancelled after finishing a test item to prevent further alert generation. As a validation of test results, vendors and hospital pharma-

Table 5 Measures taken by hospital pharmacists to prevent errors due to lacking functionality

Category	Testitems	Number of CPOEs lacking this functionality	Summary of hospital pharmacists' comments	Pharmacy checks mentioned to prevent errors due to lacking functionality
DDI	DDI due to stopping medication	5	Perceived importance differs from very relevant to irrelevant.	Clinical rules
	Period after stopping medication	4	Perceived importance differs from relevant to irrelevant. Very low incidence, only relevant for a limited number of drugs.	Visual check of patient profiles.
Dose	Frequency per day incorrect	3	Not very relevant. Check on maximum (daily) dose more important.	
	Frequency more days incorrect	4	Very relevant, especially for methotrexate.	Dose regimen of once a week proposed by the CPOE for methotrexate. Maximum dose level adjusted to very low level to assure alert generation and appearance on pharmacy checklist of overridden overdoses. Special paper prescription forms for methotrexate. Pharmacy checklist for all methotrexate prescribed (and other drugs that should be prescribed less than once a day). Pharmacy delivery for one day.
	Indication-dependent overdose	4	Not very important. Only relevant for a limited number of drugs. Problems arise due to different indication coding systems for specialists and general practitioners.	
	Overdose due to duplicate order	5	Not very relevant. Low incidence. Duplicate order signals will alert physician.	Check of overridden duplicate order alerts. Visual check of ATC-categorized patient round lists. Pharmacy delivery for one route.
	Underdose	2	Not very relevant.	
	Dose calculated with help of Denekamp scale	2	Not very important. Doses for children often based on age or formulary for children (with doses per kg bodyweight). Denekampscale not used very often.	
	Dose calculation with help of Denekamp scale not allowed	5	Not very relevant. Denekampscale not used very often.	
	Weight limit for drug dose	5	Perceived importance differs from important and handy to not important (when doses for children are based on age). Problems arise because patient weights are not always entered.	Visual check of patient profiles.

Table 5 continued

Category	Testitems	Number of CPOEs lacking this functionality	Summary of hospital pharmacists' comments	Pharmacy checks mentioned to prevent errors due to lacking functionality
CI	Yes/yes contraindication	2	Important. In Medicatie/EVS contraindication can be entered as free text and shown on patient level but no checks are performed.	
	Age	2	Not very important because alert is generated that dose check is impossible.	
	Gender	3	Perceived importance differs from not important (because errors are rare) to handy.	
	Allergy	1	Important. Problems arise because of absence of standardized allergy levels.	
	Pregnancy	2	Important, but mainly for ambulatory care.	
Other	Yes/yes renal function	2	Important.	Dose adjustment is checked when serum level measurement ordered. Clinical rules.
	Yes/yes pharmacogenetics	4	Perceived importance differs from irrelevant and nice to have to important. In several hospitals genotyping is impossible or not frequently performed. Therapeutic drug monitoring is often mentioned as a good alternative.	Therapeutic drug monitoring.
	Wrong route	5	Perceived importance differs from important to not very relevant. Several CPOEs show defined routes coupled to the drug prescribed.	Pharmacy checklist for orders with routes that have been manually adjusted.
	Serum level not measured	6	Perceived importance differs from 'nice to have' to important.	Adjusted alert texts indicating the serum level has to be measured. Serum levels checked when drug has been started or DDI alert generated. Advice for serum level measurements for dedicated drugs in case of pharmacy delivery. Clinical rules.
	Serum level too high/too low	6		Clinical rules.

cists could react to incorrect test results. For interpretation of test results, hospital pharmacists rated missing functionality.

The functionality test was a snapshot performed in January 2007 with the versions of CPOE available at the time; future functionality of the CPOEs and information in the G-standard have not been taken into account. This study focussed on patient safety and therefore did not include alerts regarding non-formulary drugs or drug costs. Neither did it include drug-food interactions nor corollary orders because food and lab ordering are minimally integrated in Dutch hospital CPOEs. The results of this study cannot be directly extrapolated to the quality of drug safety alerting in individual hospitals as implementation problems, software adjustments or local customization can result in missing alerts. All test items contributed to the same extent to the overall sensitivity and specificity but they may contribute differently to the number of alerts generated and the risk of alert fatigue. Furthermore, the nonintrusive presentation of Theriak and TPM may have a different impact on the cognitive burden on the user than pop-up alerts [16].

Notwithstanding these limitations, this study presents a comprehensive test for drug safety alerting, which may be used in hospitals all over the world to test performance. Furthermore this study gives an insight into the differences in drug safety functionality between CPOEs, which may help health care professionals and institutions to choose a CPOE system. Finally this study shows ways of addressing lacking functionality and assuring patient safety.

CONCLUSIONS

This study shows that the newly developed test is highly discriminative: it shows widely varying drug safety alerting functionality despite the use of a common knowledge base. None of the Dutch hospital CPOEs fully implemented all variables present in the Dutch drug database. Many within-order checks and patient-specific checks were present in all systems, although alerting on CIs, which is perceived to be basic clinical decision support, was absent in 2 systems. Alert generation or suppression due to new patient conditions or laboratory data was largely absent.

CPOE systems with clinical decision support may give doctors a false feeling of security, as they may not be aware of the limitations of such programs. Hospital pharmacists perceived alerting on 'frequency less than once a day incorrect' to be very important (e.g., methotrexate dosed once a day) and this functionality was missing in 4 out of the 6 systems tested. They had to perform additional pharmacy checks to compensate for missing functionality, but these measures were not always sufficient to prevent errors. TPM had the best functionality for drug safety alerting but showed alerts nonintrusively.

Until now, there has been no publicly available gold standard for objective assessment of drug safety alert functionality. With our test such an analysis can be performed easily on any CPOE system with clinical decision support, thereby making doctors and healthcare systems

aware of the limitations and potential safety risks of their software system and the risk of medication errors.

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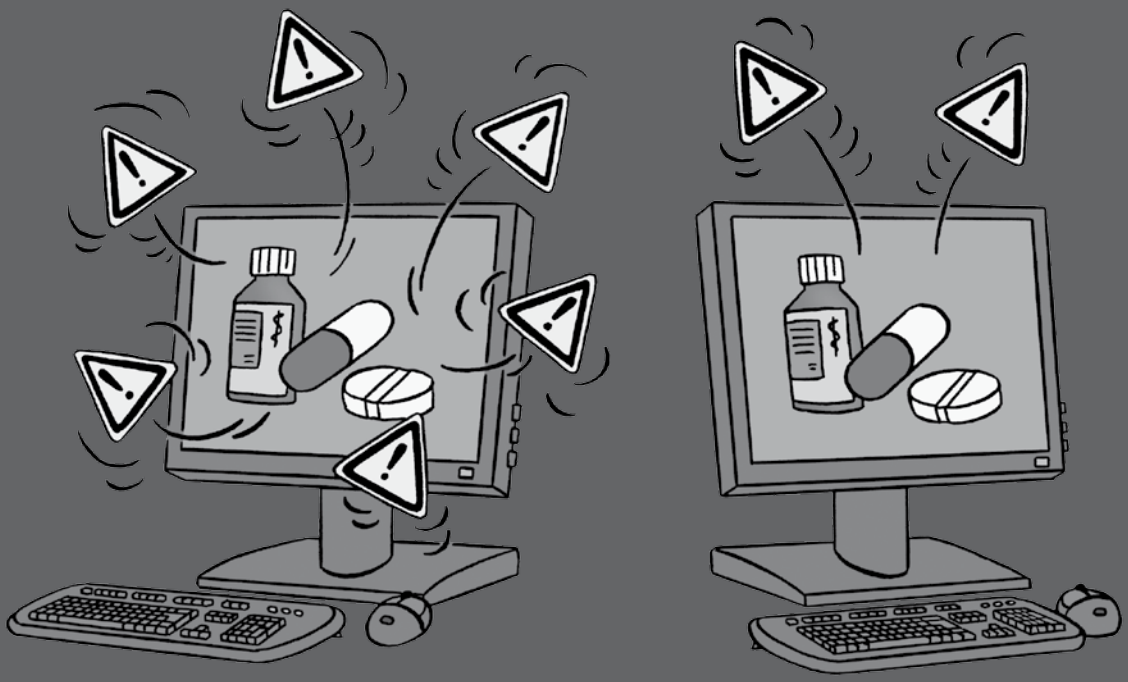
Appendix to chapter 2.4

Functionality test for drug safety alerting



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INTRODUCTION

This functionality test has been developed for testing drug safety alerting in computerized physician order entry systems (CPOEs) and consists of a sensitivity and a specificity test with 29 and 19 testitems respectively. Per testitem 3 patient cases (a, b, and c) were developed. In first instance, only the first two patient cases have to be entered. The third patient case only has to be entered in case of unambiguous or negative test results. For each testitem, entered patient cases have to show similar results (presence or absence of alerts).

The numbers between brackets mentioned in the column 'alert expected' or 'reason no alert expected' refer to the alert codes for drug-drug interactions, contraindications, renal function and pharmacogenetics in the Dutch drug database.

ENTRY OR SELECTION OF TESTPATIENTS

Five testpatients are used in this test, try to enter these testpatients in the CPOE.
A = Child, 9 years old, 30 kg, 138 cm
B = Child, 1 year old, 11 kg, 75 cm
C = Woman, 33 years old, 70 kg, 165 cm
D = Man, 42 years old, 93 kg, 182 cm
E = Child, 1 month old, 4 kg, 60 cm

If it appears to be impossible to enter new test patients, select patients in the following ranges:
A = Child, 7-10 years old, 25-33 kg, 130-150 cm
B = Child, 6-18 months old, 7-15 kg, 70-100 cm
C = Woman, 21-45 years old, 55-75 kg, 152-175 cm
D = Man, 22-45 years old, 65-100 kg, 165-200 cm
E = Child, 1-4 months old, 3-6 kg, 50-70 cm

SENSITIVITY TEST

Start with the first patient case (a) and enter it completely. In case of alert generation, score the case as positive (+), override the alert and complete the order (if possible). If no alert is generated, score the case as negative (-). After entry of both patient cases (a and b), delete them before starting with the following testitem. The third patient case only has to be entered in case of unambiguous results, unexpected negative results and turning on functionality.

Patient	Testitem	Alert expected	Alert? +/-	Remarks
	Patient cases			
Within order checks				
C	1. Overdose	Dose too high Max dose =		
	a. Levothyroxine tablet 25μg (Thyrax®); 275 μg per os once daily	1dd 250 μg		
	b. Carbamazepin suspension 20mg/ml (Tegretol®);1000mg per os twice daily	2dd 900 mg		
	c. Temazepam tablet 10mg; 60 mg per os once daily	1dd 40 mg		
C	2. Overdose combination product	Dose too high Max dose =		
	a. Co-amoxiclav tablet 500mg/125mg (Augmentin®); 3 tablets 500/125= 1500mg/375mg per os thrice daily	3dd 1000mg/250mg		
	b. Salmeterol/fluticason dose aerosol 25μg/50μg (Seretide®); 3 puffs thrice daily per inhalation	2dd 50μg /100μg		
	c. Piperacillin/tazobactam injection powder 4000mg/500mg (Tazocin®); 8000mg/1000mg iv 4 times a day	4dd 4500mg/563mg		
C	3. Frequency per day incorrect	Frequency incorrect Max frequency =		
	a. Paracetamol tablet 500mg; 500 mg per os 8 times a day	Six times a day		
	b. Salmeterol dose aerosol 25μg; 1 puff per inhalation 8 times a day	Twice daily		
	c. Flunitrazepam tablets 1mg; 0.5 mg 6 times daily orally	Once daily		
C	4. Frequency less than once a day incorrect	Frequency incorrect Max frequency =		
	a. Fentanyl plaster 25 μg/hour (Durogesic®); one plaster cutaneously once daily	Once per 2 days		
	b. Methotrexate tablet 2.5mg; 7.5 mg per os once daily	Thrice weekly		
	c. Alendronic acid tablet 70mg (Fosamax®); 70 mg per os once daily	Once a week		

Patient	Testitem	Alert expected	Alert? +/-	Remarks
	Patient cases			
C	5. Underdose	Dose too low Min dose =		
	a. Amoxicillin capsule 375mg; 375 mg per os twice daily	2dd 500mg		
	b. Piperacillin injection powder 2000mg; 1000mg iv thrice daily	3dd 2000mg		
	c. Erythromycin suspension powder 500mg; 250 mg per os once daily	2dd 500mg		
C	6. Wrong route	Wrong route Correct route =		
	a. Paracetamol suppository 1000mg; 1000 mg per os once daily	Rectally		
	b. Diclofenac coated tablet 50mg (Cataflam®); 50 mg iv once daily	Per os		
	c. Morphin tablet retard 10mg (MS Contin®); 10 mg rectally four times daily	Per os		
A	7. Overdose due to duplicate order	Alert should mention addition of doses		
	a1. Morphin tablet retard 10mg (MS Contin®); 10 mg per os twice daily a2. Morphin suppository 10mg; 10 mg rectally thrice daily			
	b1. Diclofenac coated tablet 50mg (Cataflam®); 50 mg per os thrice daily b2. Diclofenac suppository 100mg ; 100 mg rectally twice daily			
	c1. Paracetamol tablet 500mg; 500 mg per os thrice daily c2. Paracetamol suppository 1000 mg; 1000mg rectally twice daily			
D	8. Duplicate order irrational	Duplicate order		
	a1. Simvastatin tablet 20mg; 20 mg once daily orally a2. Simvastatin tablet 10mg (Zocor®); 10 mg once daily orally	Two simvastatin prescriptions		
	b1. Bumetanide tablet 1mg; 1 mg thrice daily orally b2. Bumetanide injection 1mg (Burinex®); once 1mg intravenously	Two bumetanide prescriptions		
	c1. Morphin tablet retard 10mg (MS Contin®); 10 mg per os six times a day c2. Morphin suppository 10 mg; 10 mg rectally four times a day	Two morphin prescriptions		

Patient	Testitem	Alert expected	Alert? +/-	Remarks
	Patient cases			
D	9. Pseudo-duplicate order irrational (irrational combination of comparable drugs)	Duplicate order		
	a1. Ramipril tablet 1.25mg; 2.5 mg per os once daily a2. Losartan tablet 50mg (Cozaar®), 50 mg per os once daily	Two prescriptions for RAAS inhibition		
	b1. Simvastatin tablet 20mg; 20 mg per os once daily b2. Atorvastatin tablet 20mg (Lipitor®); 20 mg per os once daily	Two prescriptions for cholesterol lowering		
	c1. Ibuprofen coated tablet 200mg (Advil®); 200 mg per os once daily c2. Diclofenac coated tablet 50mg (Cataflam®); 50 mg per os once daily	Two prescriptions for NSAIDs		
D	10. Yes/yes drug-drug interaction (DDI)	DDI		
	a1. Tramadol effervescent tablet 50mg; 50 mg per os thrice daily a2. Fluoxetine tablet 20mg; 20 mg per os once daily	Increased risk serotonin syndrome (4227)		
	b1. Simvastatin tablet 20mg; 20 mg per os once daily b2. Claritromycin tablet slow release (Klacid®); 500 mg per os once daily	Increased risk myopathy and rhabdomyolysis (2763)		
	c1. Lithium carbonate capsules 100mg; 200 mg per os once daily c2. Enalapril tablet 10mg (Renitec®); 10 mg per os once daily	Increased serum level Li (1163)		
D	11. Yes/yes sequence-dependent drug-drug interaction	DDI		
	a1. Bumetanide tablet 1mg; 1 mg per os thrice daily a2. Ramipril tablet 2.5mg; 2.5 mg per os once daily	Severe hypotension if ACE inhibitor is added to patient on diuretics (19)		
	b1. Hydrochlorthiazid tablet 25mg; 25 mg per os once daily b2. Enalapril tablet 10mg (Renitec®); 10 mg per os once daily	Ibid (19)		
	c1. Bumetanide tablet 1mg; 1 mg per os thrice daily c2. Losartan tablet 50 mg (Cozaar®); 50 mg per os once daily	Severe hypotension if AT antagonist is added to patient on diuretics (1228)		

Patient	Testitem	Alert expected	Alert? +/-	Remarks
	Patient cases			
D	12. Drug-drug interaction due to stopping medication	DDI		
	a1. Phenytoin tablet 100mg (Diphantoin®); 100 mg per os once daily a2. Fluoxetine tablet 20 mg; 20 mg per os once daily, stopdate one month later	Decreased serum level phenytoin after stopping fluoxetine (876)		
	b1. Ciclosporin potion 100mg/ml (Neoral®); 130 mg=1,3 ml per os twice daily b2. Erythromycin tablet 250mg (Erythrocine®); 500 mg per os twice daily, stopdate one month later	Decreased serum level ciclosporin after stopping CYP3A4-inhibitor (434)		
	c1. Tizanidin tablet 4mg (Sirdalud®); 4mg per os thrice daily c2. Fluvoxamin tablet 50mg; 150 mg per os once daily, stopdate one month later	Increased serum level tizanidine after stopping CYP1A2-inhibitor (5878)		
D	13. Drug-drug interaction; period after stopping medication	DDI		
	a1. Fluoxetine 20mg; 20 mg per os once daily, stopdate one day later a2. Tranylcypromin 10mg; 10 mg per os once daily, startdate equal to stopdate fluoxetine	Risk of developing serotonin syndrome; interval of 5 weeks required (3514)		
	b1. Fluoxetine 20mg; 20 mg per os once daily, stopdate one day later b2. Phenelzin 15mg (Nardil®); 15 mg per os once daily, startdate equal to stopdate fluoxetine	Ibid (3514)		
	c1. Citalopram tablet 20mg; 20 mg per os once daily, stopdate one day later c2. Moclobemid tablet 150mg; 150 mg per os twice daily, startdate equal to stopdate citalopram	Risk of developing serotonin syndrome; interval of 2 weeks required (3522)		
D	14. Yes/yes time-dependent drug-drug interaction	DDI		
	a1. Algeldrate/magnesiumoxide chew tablet 200/400mg(Maalox®); 1 tablet per os once daily at 8.00 am a2. Ciprofloxacin tablet 250mg (Ciproxin®); 250 mg per os twice daily at 8.00 am and 8.00 pm	Ciprofloxacin 4 hours before antacid to prevent absorption reduction (906)		
	b1. Minocyclin tablet 100mg; 100mg per os once daily at 8.00 am b2. Ferro fumarate 200mg; 200 mg per os once daily at 8.00 am	Minocyclin 2 hours before iron to prevent absorption reduction (1562)		
	c1. Alendronic acid tablet 10mg (Fosamax®); 10 mg per os once daily at 8.00 am c2. Algeldrate/magnesiumoxide chew tablet 200/400mg (Maalox®); 1 tablet per os once daily at 8.00 am	Alendronic acid half an hour before antacid to prevent absorption reduction (2135)		

Patient	Testitem	Alert expected	Alert? +/-	Remarks
	Patient cases			
Patient-specific checks				
A	15. Overdose per kg body weight	Dose too high Max/kg per dose (max absolute dose)		
	a. Morphin tablet retard 15mg (MS Contin®); 0.5 mg/kg per os twice daily (15 mg)	0.4 mg/kg (max 20mg)		
	b. Doxycyclin tablet 100mg (Doxy Disp PCH ®); 5 mg/kg per os once daily (150 mg)	4 mg/kg (max 200mg)		
	c. Flucloxacillin 500mg; 35 mg/kg per os thrice daily (1000 mg)	33 mg/kg (max 1333mg)		
A	16. Overdose per m^2 body surface area	Dose too high Max dose/m^2 =		
	a. Aciclovir infusion 25mg/ml; 1000 mg/m^2 iv thrice daily	3dd 500 mg/m^2		
	b. Amsacrine infusion 50mg/ml (Amsidine®); 200 mg/m^2 iv once	120 mg/m^2		
	c. Doxorubicin infusion 2mg/ml (Doxorubin®); 40 mg/m^2 iv once a week	30 mg/m^2		
A	17. Weight limit for drug dose	Drug has to be dosed on body weight below indicated weight		
	a. Atomoxetine capsule 10mg (Strattera®); 80 mg per os once daily	< 70 kg 1.2 mg/kg		
	b. Azitromycin tablet 500mg; 500 mg per os twice daily	< 45kg 2dd 10 mg/kg		
B	c. Cefuroxim suspension 25 mg/ml (Zinnat®); 250mg=10 ml per os twice daily	<16 kg 2dd 15 mg/kg		
A	18. Dose calculated with help of Denekamp scale	No dose available < 18 years. Dose calculation with help of Denekamp scale allowed <16 years		
	a. Sildenafil tablet filmcoated 20mg (Revatio®); 75 mg per os once daily			
	b. Frusemide tablet 40mg; 60 mg per os once daily			
	c. Alfuzosin tablet retard 60mg; 60 mg per os once daily			

Patient	Testitem	Alert expected	Alert? +/-	Remarks
	Patient cases			
E	19. Dose calculation with help of Denekamp scale not allowed	Min age for dose calculation =		
	a. Sildenafil tablet filmcoated 20mg (Revatio®); 75 mg per os once daily	6 months		
	b. Frusemide tablet 40mg; 60 mg per os once daily	6 months		
	c. Alfuzosin tablet retard 60mg; 60 mg per os once daily	6 months		
D	20. Indication-dependent overdose	Dose too high Max dose for this indication =		
	a. Metoprolol tablet 50mg; 200 mg per os twice daily for cardiac failure	50 mg		
	b. Dexamethason capsule 10mg; 40mg per os once daily for inflammation in general care	15 mg		
	c. Colchicin tablet 0.5mg; 2mg per os once daily for gout	1.5 mg		
C	21. Yes/yes contraindication			
	a. Enter: patient has a depression. Mefloquine tablet 250mg (Lariam®); 500mg per os thrice daily	Mefloquin may induce depression (1283)		
	b. Enter: patient has asthma. Propranolol capsule retard 80mg; 80 mg per os once daily	Propranolol may induce broncho-constriction (74)		
	c. Enter patient has G6PD-deficiency. Primaquin capsule 15mg; 15 mg per os once daily	Primaquine may induce acute hemolysis (191)		
C	22. Contraindication allergy	Contraindicated in patients with penicillin allergy		
Enter: patient has a penicillin allergy				
	a. Amoxicillin capsule 500mg; 500 mg per os once daily			
	b. Piperacillin injection powder 2000mg; 1000mg iv once daily			
	c. Enter patient has a sulfonamid allergy. Sulfadiazin suspension 100mg/ml; 2000 mg per os once daily			

Patient	Testitem	Alert expected	Alert? +/-	Remarks
	Patient cases			
C	23. Contraindication pregnancy	Contraindicated during pregnancy		
Enter: patient is pregnant				
	a. Doxycyclin capsule 100mg (Doxy Disp PCH®) ; 100mg per os once daily, first day 200mg once	(107)		
	b. Isotretinoin capsule 20mg; 40 mg per os once daily	(118)		
	c. Primaquin capsule 15mg; 15 mg per os once daily	(722)		
	24. Contraindication gender	Contraindicated in		
C	a. Select testpatient C. Testosteron capsule 40mg (Andriol®); 80 mg per os twice daily	females		
D	b. Select testpatient D. Estradiol vaginal tablet 25μg (Vagifem®); 25 μg vaginally once daily for two weeks	males		
D	c. Select testpatient D. Ethinylestradiol/levonorgestrel tablet 30/150μg (Microgynon 30®); 1 tablet per os once daily for 21 days, then stop 7 days	males		
B	25. Contraindication age	Contraindicated in age <		
	a. Loperamid capsule (Imodium®); 2mg per os once daily	2 years		
	b. Doxyclin tablet 100mg (Doxy Disp PCH®); 100mg per os once daily	8 years		
	c. Norfloxacin tablet 400mg; 400mg per os once daily	16 years		
C	26. Yes/yes renal function	Contraindicated or dose adjustment required in case of bad renal function		
Enter: patient has a glomerular filtration rate (GFR) of 15 ml/min				
	a. Celecoxib capsule 100mg (Celebrex®); 100mg per os twice daily	Risk of acute renal failure in case of GFR= 30 ml/min (1299)		
	b. Metformin tablet 500mg; 500mg per os thrice daily	Contraindicated if GFR 10-30 ml/min (557)		
	c. Auranofin tablet 3mg (Ridaura®); 3mg per os twice daily	Contraindicated if GFR < 50 ml/min (347)		

Patient	Testitem	Alert expected	Alert? +/-	Remarks
	Patient cases			
C	27. Yes/yes pharmacogenetics	Genetic variation requiring action		
Enter: patient is poor metabolizer of CYP2D6				
	a. Clomipramin tablet 25mg; 75 mg per os twice daily	Adjust to 50% of normal dose and measure serum levels (1480)		
	b. Risperidon tablet 2mg; 2mg per os once daily	Select an alternative drug or monitor adverse events (1537)		
	c. Haloperidol tablet 5mg (Haldol®); 5 mg per os once daily	Adjust to 50% of normal dose or select an alternative (1552)		
Checks related to laboratory data and new patient conditons				
C	28. Serum level not measured	Serum level measurement required for		
	a1. Captopril tablet 50mg; 50 mg per os once daily a2. Spirinolacton tablet 50mg; 50 mg once daily orally	K		
	b. Lithium carbonate capsule 100mg; 400 mg per os once daily	Li		
	c. Acenoucoumarol tablet 1mg; 4mg per os once	International Normalized Ratio (INR)		
Do not delete these orders before finishing testitem 29.				
C	29. Serum level too high	Serum level too high		
	a. Enter Serum level K = 7 mmol/L			
	b. Enter Serum level Li = 3 mmol/L			
	c. Enter INR (international normalized ratio) = 5			

SPECIFICITY TEST

Start with the first case (a) and enter it completely. In case of no alert being generated, score the case as positive. If an alert is generated, score the case as negative, override the alert and complete the order (if possible). After entry of both cases (a and b), delete them before starting with the following testitem. The third case only has to be entered in case of unambiguous results, unexpected alerting and turning off functionality.

Patient	Testitem	Reason no alert expected	No alert? +/-	Remarks
	Patient cases			
Within order checks				
D	1. No/no drug-drug interaction	DDI not proven		
	a1. Acetylsalicylic acid tablet 500mg; 1000 mg per os once daily a2. Clopidogrel filmcoated tablet 75mg (Plavix®); 75 mg per os once daily	(5398)		
	b1. Bisacodyl tablet 5mg; 5 mg per os once daily b2. Algeldrate/magnesiumoxide chew tablet 200/400mg (Maalox®); 1 tablet per os once daily	(2321)		
	c1. Phenytoin tablet 100mg (Diphantoin®); 200 mg per os once daily c2. Fluvoxamin tablet 50mg; 150 mg per os once daily	(4480)		
D	2. Yes/no drug-drug interaction	DDI not requiring action		
	a1. Clozapine tablet 25mg; 175 mg per os once daily a2. Risperidone tablet 0.5mg (Risperdal®); 5mg per os once daily	(3654)		
	b1. Digoxin tablet 0.25mg (Lanoxin®); 0.25 mg per os once daily b2. Frusemide tablet 40mg; 40 mg per os once daily	(817)		
	c1. Bosentan tablet 62.5mg (Tracleer®); 62.5 mg per os twice daily c2. Simvastatin tablet 20mg; 20 mg per os once daily	(4685)		
D	3. No/no sequence-dependent drug-drug interaction	DDI not requiring action if combined in this direction		
	a1. Enalapril tablet 10mg (Renitec®); 10 mg per os once daily a2. Hydrochlorthiazid tablet 25mg; 25 mg per os once daily	No severe hypotension if diuretic is added in patient on ACE inhibitors (19)		
	b1. Ramipril tablet 2.5mg; 2.5 mg per os once daily b2. Bumetanide tablet 1mg; 1 mg per os thrice daily	Ibid (19)		
	c1. Captopril tablet 50mg; 50 mg per os once daily c2. Chlortalidon tablet 25mg; 25 mg per os once daily	Ibid (19)		

Patient	Testitem	Reason no alert expected	No alert? +/-	Remarks
	Patient cases			
D	4. Yes/yes time-dependent drug-drug interaction			
	A1. Algeldrate/magnesiumoxide chew tablet 200/400mg (Maalox®); 1 tablet per os once daily at 8.00 am A2. Ciprofloxacin tablet 250mg (Ciproxin®); 250 mg per os twice daily at 12.00 am and 18.00 pm	No absoption reduction if ciprofloxacin 4 hours before antacid (906)		
	B1. Minocyclin tablet 100mg; 100mg per os once daily at 8.00 am B2. Ferrofumarate tablet 200mg; 200 mg per os once daily at 12.00 am	No absorption reduction if minocyclin 2 hours before iron (1562)		
	C1. Alendronic acid tablet 10mg (Fosamax®); 10 mg per os once daily at 8.00 am C2. Algeldrate/magnesiumoxide chew tablet 200/400mg (Maalox®); 1 tablet per os once daily at 12.00 am	No absorption reduction if alendronic acid half an hour before antacid (2135)		
D	5. Duplicate order systemic-oral (irrelevant)	Irrelevant duplicate order		
	A1.Hydrocortisone tablet 20mg; 20 mg per os once daily A2. Hydrocortisone cream 1%; thin application twice daily			
	B1. Budesonid dose aerosol 200μg (Pulmicort®); 1 puff per inhalation once daily B2. Budesonid capsule retard 3mg; 3 mg per os once daily			
	C1. Erytromycin suspension granulate 500mg; 500 mg per os twice daily C2. Erytromycin ocular ointment 0.5%; 1 cm applied on eyelid once daily			
D	6. Pseudo-duplicate order rational (rational combination of comparable drugs)	Rational drug combination		
	A1. Insulin regular 100 IE/ml (Actrapid®); 10 IE sc thrice daily A2. Insulin detemir penfill 100 IE/ml (Levemir®); 10 IE sc once daily ante noctem			
	B1. Salbutamol dose aerosol 100μg (Ventolin®); 1 puff per inhalation twice daily B2. Salmeterol dose aerosol 50μg (Salmeterol®); 1 puff per inhalation once daily			
	C1. Timolol eyedrops 0.1% (Timoptol®); 1 drop in left eye twice daily C2. Metoprolol tablet 100mg; 100 mg per os once daily			

Patient	Testitem	Reason no alert expected	No alert? +/-	Remarks
	Patient cases			
Patient-specific checks				
A	7. Weight limit for drug dose	Dosing per kg not necessary for weight		
Change body weight to 80 kg				
	a. Atomoxetine capsule 10mg (Strattera®); 80 mg per os once daily	> 70kg		
	b. Azitromycin tablet 500mg; 500 mg per os twice daily	> 45 kg		
	c. Cefuroxim suspension 25mg/ml (Zinnat®); 250mg=10ml per os twice daily	> 16 kg		
C	8. Indication-dependent overdose	Max dose for this indication		
	a. Metoprolol tablet 50mg; 200mg per os once daily for angina pectoris	200 mg		
	b. Dexamethason capsule 10mg; 40 mg per os once daily for malignancy with unknown localisation	40 mg		
	c. Colchicin tablet 0.5mg; 2 mg per os once daily for familiar mediterranean fever	2 mg		
D	9. No/no contraindication	Contraindication not proven		
	a. Enter: patient has a depression. Acebutolol tablet 200mg; 200 mg per os twice daily	(1279)		
	b. Enter: patient has asthma. Betahistine tablet 8mg; 8 mg per os thrice daily	(561)		
	c. Enter: patient has a depression. Digoxin tablet 0.25mg (Lanoxin®); 0.25 mg per os once daily	(1282)		
	10. Contraindication gender	Not contraindicated in		
C	a. Select testpatient C. Estradiol vaginal tablet 25µg (Vagifem®); 25 µg vaginally once daily for two weeks	females		
D	b. Select testpatient D. Testosteron capsule 40mg (Andriol®); 40 mg per os twice daily	males		
C	c. Ethinylestradiol/levonorgestrel tablet 30/150µg (Microgynon 30®); 1 tablet per os once daily for 21 days, then stop 7 days	females		
C	11. No/no renal function	No dose adjustments required if GFR > 10 ml/min		
Enter patient has a glomerular filtration rate of 20 ml/min				
	a. Flunitrazepam tablet 1mg; 0.5mg per os once daily	(1521)		
	b. Doxycyclin tablet 100mg (Doxy Disp PCH®); 100 mg per os once daily	(1387)		
	c. Amlodipine tablet 10mg; 10 mg per os once daily	(1451)		

Patient	Testitem	Reason no alert expected	No alert? +/-	Remarks
	Patient cases			
C	12. Yes/no renal function	No dose adjustments required if GFR > 10 ml/min		
Enter patient has a glomerular filtration rate (GFR) of 20 ml/min				
	a. Diazepam tablet 10mg; 10 mg per os once daily	(1520)		
	b. Tolbutamide tablet 500mg; 500 mg per os once daily	(1240)		
	c. Propranolol capsule retard 80mg; 80 mg per os once daily	(1297)		
C	13. Normal renal function	No dose adjustment required if GFR>		
Enter patient has a glomerular filtration rate of 75 ml/min				
	a. Celecoxib capsule 100mg (Celebrex®); 100 mg per os twice daily	30 ml/min (1299)		
	b. Metformin tablet 500mg; 1500mg per os thrice daily	50 ml/min (557)		
	c. Auranofin tablet 3mg; 3 mg per os twice daily	50 ml/min (347)		
C	14. No/no pharmacogenetics	Pharmacogenetic interaction not proven		
Enter patient is an intermediate metabolizer for CYP2D6				
	a. Clozapine tablet 25mg; 25 mg per os once daily	(1530)		
	b. Flupentixol coated tablet 5mg; 5mg per os thrice daily	(1532)		
	c. Enter patient is ultrarapid metabolizer for CYP2D6. Olanzapine tablet 10mg (Zyprexa®); 10 mg per os once daily	(1562)		
C	15. Yes/no pharmacogenetics	No action required		
Enter patient is an intermediate metabolizer for CYP2D6				
	a. Haloperidol tablet 5mg (Haldol®); 5 mg per os once daily	Only action required for ultrarapid and poor metabolizers (1551)		
	b. Paroxetin tablet 20mg; 20mg per os once daily	Only action for ultrarapid metabolizers (1563)		
	c. Tamoxifen tablet 40mg; 40 mg per os once daily	No action required (1602)		
C	16. Normal pharmacogenetics	No contraindications and no dose adjustment required if normal pharmacogenetics		
Enter: patient is a normal metabolizer for CYP2D6				
	a. Clomipramin tablet 25mg; 75 mg per os once daily			
	b. Risperidon tablet 2mg (Risperdal®); 2 mg per os twice daily			
	c. Haloperidol tablet 5mg (Haldol®); 5 mg per os once daily			

Patient	Testitem	Reason no alert expected	No alert? +/-	Remarks
	Patient cases			
Checks related to laboratory data and new patient conditions				
D	17. Yes/yes contraindication deleted	No action required if contraindication deleted		
	a. Enter: patient has a depression. Then delete contraindication depression. Mefloquin tablet 250mg (Lariam®); 500 mg per os thrice daily	(1283)		
	b. Enter patient has asthma. Then delete contraindication asthma. Propranolol tablet retard 80mg; 80 mg per os once daily	(74)		
	c. Enter patient has G6PD-deficiency. Then delete contraindication G6PD-deficiency. Primaquin capsule 15mg; 15 mg per os once daily	(191)		
C	18. Contraindication pregnancy deleted	No action required if contraindication deleted		
Enter patient is pregnant and lactates. Then delete contraindication pregnancy and lactation.				
	a. Doxycyclin capsule 100mg (Doxy Disp PCH®); 100 mg per os once daily, first day 200 mg			
	b. Isotretinoin capsule 20mg; 40 mg per os once daily			
	c. Primaquin capsule 15mg; 15 mg per os once daily			
D	19. Serum level measured	No alert required if serum levels below		
	a. Enter: serum level K = 3.5 mmol/L a1. Captopril tablet 50mg; 50 mg per os once daily a2. Spirinolacton tablet 50mg; 50 mg per os once daily	K < 5 mmol/L		
	b. Enter: serum level Li = 1 mmol/L Lithium carbonate capsule 100mg; 400 mg per os once daily	Li < 1.2 mmol/L		
	c. Enter: INR= 3. Acenocoumarol tablet 1mg; 4mg per os once	INR < 3.5		

Chapter 3

Decreasing the burden of excessive numbers of drug safety alerts

Chapter 3.1

Turning off frequently overridden drug alerts: limited opportunities for doing it safely

Heleen van der Sijs, Jos Aarts, Teun van Gelder, Marc Berg, Arnold Vulto

ABSTRACT

Objective: This study sought to identify opportunities to safely turn off frequently overridden drug-drug interaction alerts (DDIs) in computerized physician order entry (CPOE).

Design: Quantitative retrospective analysis of drug safety alerts overridden during 1 month and qualitative interviews with 24 respondents (18 physicians and 6 pharmacists) about turning off frequently overridden DDI alerts, based on the Dutch drug database, in a hospital setting. Screen shots and complete texts of frequently overridden DDIs were presented to physicians of internal medicine, cardiology, and surgery and to hospital pharmacists who were asked whether these could be turned off hospital-wide without impairing patient safety, and the reasons for their recommendations.

Results: Data on the frequency of alerts overridden in 1 month identified 3,089 overrides, of which 1,963 were DDIs. The category DDIs showed 86 different alerts of which 24 frequently overridden alerts, accounting for 72% of all DDI overrides, were selected for further evaluation. The 24 respondents together made 576 assessments. Upon investigation, differences in the reasons for turning off alerts were found across medical specialties and among respondents within a specialty. Frequently mentioned reasons for turning off were 'alert well known,' ' alert not serious' or 'alert not needing (additional) action', or that the effects of the combination were monitored or intended. For none of the alerts did all respondents agree that it could be safely turned off hospital-wide. The highest agreement was 13 of 24 respondents (54%). A positive correlation was found between the number of alerts overridden and the number of clinicians recommending to turn them of.

Conclusion: Although the Dutch drug database is already a selection from all DDIs mentioned in literature, the majority of respondents wanted to turn off DDI alerts to reduce alert overload. Turning off DDI alerts hospital-wide appeared to be problematic because of differences among physicians of drug-related knowledge and of differences across the hospital in routine drug monitoring practices. Furthermore, several reasons for suppression of alerts could be questioned from a safety perspective. Further research should investigate when each of the following might help: changes in alert texts; new differential alert triggers based on clinician knowledge or specialty; and nonintrusive alert presentation so long as serum levels and patient parameters are measured and stay within limits.

INTRODUCTION

Computerized physician order entry (CPOE) systems frequently include integrated decision support components. The generation of alerts depends on whether information (on drug-drug interactions or dose levels) is present in the CPOE system's knowledge base and whether the system can use this information (alerting features). Knowledge bases are often overly inclusive, generating alerts for every potentially dangerous situation mentioned in the literature [1-4]. An overly inclusive database may generate excessive numbers of drug safety alerts, causing clinicians to ignore even important alerts and to override them, potentially impairing patient safety [3,5]. The most important reason listed by physicians for overriding alerts is alert fatigue, which often occurs because some alerts do not relate to serious outcomes, because many alerts are irrelevant, and because a given alert may appear repeatedly. To reduce alert fatigue and to improve patient safety, irrelevant and nonurgent alerts should be suppressed or displayed in a noninterruptive manner [5]. However, turning off alerts can also impair patient safety if performed without careful error management [5,6]. This study attempted to identify situations in which frequently overridden drug alerts within a CPOE system might potentially be suppressed in some manner, while at the same time maintaining safety.

Research questions included:

1. What reasons do hospital clinicians give when they are asked whether drug safety alerts can be safely turned off hospital-wide?
2. Do different specialties differ in their opinions and considerations on this question?
3. Do residents and specialists differ in their opinions and considerations regarding turning off drug safety alerts?
4. Does the desire to turn off a drug safety alert change if more information about the alert is presented?
5. Which frequently overridden drug safety alerts can be safely turned off hospital-wide?

BACKGROUND

Error management has three components: prevention, visible notification of potential and real errors, and mitigation of the effects of errors [7,8]. Drug safety alerting systems provide visible notification of potential errors during the order entry process, with the goal of averting such errors. To limit the incidence of potentially dangerous prescribing errors, alerts should be generated in all critical situations; high sensitivity is strived for. Alerting per se does not automatically prevent all critical errors because cognitive overload induced by overactive alerting systems is itself a known cause of errors [9]. Alarms that are installed on a 'better safe than sorry' basis are likely to make responses to them less rather than more reliable [10]. High numbers of low-importance and irrelevant alerts are common causes of alert fatigue [5]. The importance

or relevance of an alert is not absolute, but rather situation-dependent. An alert may become irrelevant in a hospital where monitoring of serum drug levels or clinical effect-related patient parameters occurs routinely, whereas it may be relevant for the general practitioner who does not routinely monitor such parameters in outpatient settings.

The current study attempted to identify opportunities to turn off inpatient drug-related alerts safely. Feldstein et al. [11] stated that clinicians should not be able to control the display of safety alerts because those who need alerts the most would turn them off. It seems desirable to consult physicians of different specialties before turning off alerts because this may reveal important considerations for the improvement of computerized decision support systems (CDSS). Another consideration is that uninformed suppression of drug alerts could result in legally actionable negligence claims when harm to patients occurs that might have been prevented. Kuperman et al. [4] pleaded for research targeting an improved understanding of how to employ commercial knowledge bases to create CDSS that are well accepted by practicing clinicians.

In their viewpoint paper, Miller et al. [1] argued for a U.S. national standard for drug interaction information, that could be locally customized, and included: (1) generic names of interacting drugs, (2) a brief human-readable but computable standard set of descriptions for the clinical nature of the interactions, (3) an indication of the strength of the evidence base for the interaction/effect on a five-category scale, (4) a four-category scale for the seriousness of interaction/effects, and (5) a frequency listing on a logarithmic scale of how often each severity reaction has been reported to occur.

In the Netherlands, such a national drug database exists, although some small differences from Miller et al.'s proposed criteria are discernable. The Dutch seriousness index has six categories (A through F) instead of four, and the evidence index has the same number of categories but ranges from zero to four instead of one to five [12]. A seriousness index and evidence index are combined in an alphanumeric code. Information on the frequency of adverse events often cannot be presented because of the lack of interaction studies. In the Dutch drug database (also known as G-standard) combinations of drugs mentioned in the literature as causing drug-drug interactions (DDIs) are categorized as yes/yes (interacting and requiring action), yes/no (interacting but requiring no action) and no/no (not interacting, requiring no action) [12]. Sixty-four percent of the DDIs were categorized as yes/yes DDI, automatically generating a DDI alert in the Dutch CPOE systems [12]. DDIs with the label yes/no normally do not generate alerts, but such alerts can optionally be enabled. The national Dutch drug database does contain some additional information desirable for optimizing alert specificity, such as sequence indications that indicate an alert is relevant when new drug A is added to an existing regimen containing drug B, but not if new drug B is added to existing drug A (for example, starting an angiotensin-converting enzyme inhibitor in a patient using diuretics may cause severe hypotension and should be performed with low doses, whereas a patient chronically taking angiotensin-

converting enzyme inhibitors can start with diuretics without such precautionary measures). Several CPOE systems lack the ability to use these indications for sequence-dependent alerting.

In the Netherlands, the Royal Dutch Association for the Advancement of Pharmacy generates dedicated alert texts (as well as background information) for general practitioners, community pharmacies, and hospitals. The alert texts consist of information about the potential adverse reaction (e.g., rising serum level, hypotension) and a recommendation for how to address the alerting condition, followed by extra information such as clinical consequences, mechanism or literature references. Text wording may be modified based on comments from clinical users about the texts.

The investigators hypothesized that alerts with a low level of seriousness or alerts to initiate what is already routinely performed monitoring would generate considerable agreement regarding alert suppression (i.e., turning them off). Furthermore, investigators expected that surgical and non-surgical specialties would come to different decisions (because of differences in perceived importance of drugs) and that within-specialty differences would be small. Finally, investigators hypothesized that presentation of more information about the alert will result in a decision change in less familiar alerts.

METHODS

Setting

The Erasmus University Medical Center (Erasmus MC) in Rotterdam, the Netherlands, comprises a 1237-bed academic medical center consisting of 3 hospitals, a 800-bed general hospital, a pediatric hospital, and an oncology clinic. The current study was performed in the general hospital. In that hospital, a CPOE system for medication ordering was introduced in December 2001. Since March 2005, all inpatient wards excluding the intensive care units have used the CPOE system Medicatie/EVS® by iSOFT (Leiden, the Netherlands) [13]. Physicians and midwives exclusively enter medication orders. At present, nurses are not legally allowed to prescribe drugs and therefore do not enter medication orders via CPOE. The system requires complete orders containing drug name, dosage form, strength, drug dose, frequency, start date, and start time. During order entry, medications can be selected from the pharmacy database listing stock held on the ward and in the hospital pharmacy, or from the national drug database. It is also possible to select preformed, standardized orders from predefined order sets, or to enter free text prescriptions [13]. The CPOE system generates intrusive (stopping user workflow) drug safety alerts for DDIs, for overdosages, and for duplicate orders. Figure 1 shows how an alert is shown to the user: both interacting drugs, their dosage regimens, and an explanation including a recommendation are given. The complete alert text can only be read if the user scrolls down to the bottom. In Medicatie/EVS® version 2.20, which has been used in this study, alerts can always be overridden without giving a reason. Overridden alerts are routinely logged for

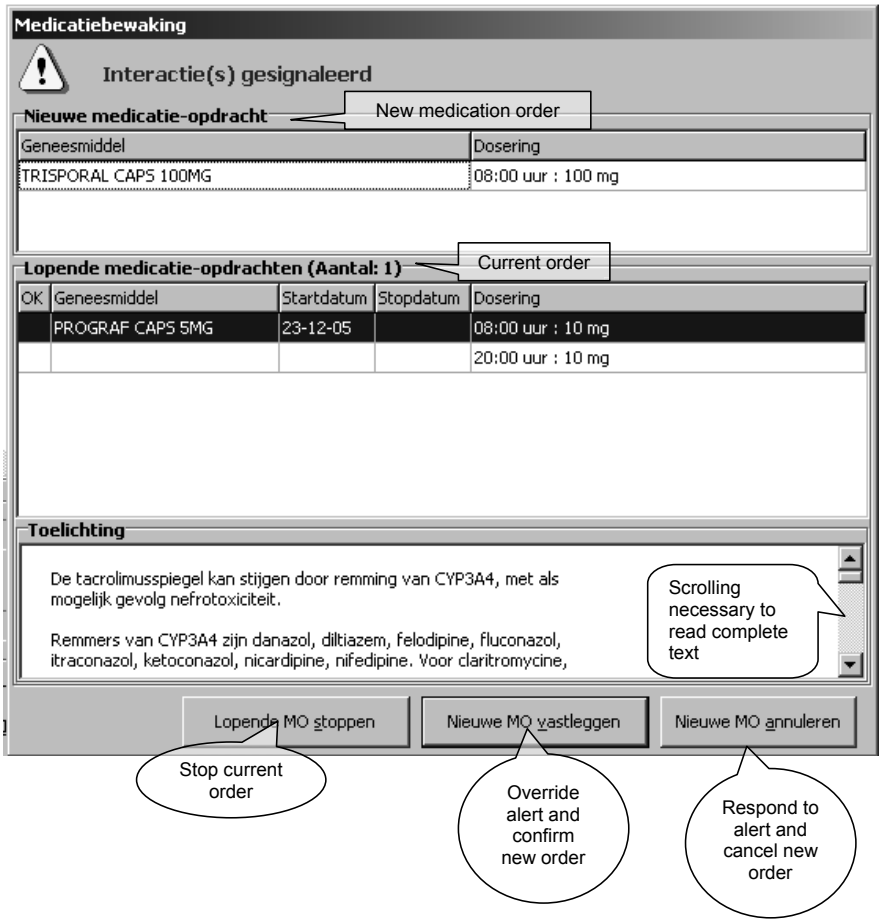

Figure 1 Example of a screenshot of a drug-drug interaction (DDI)
DDI alert presented to a physician ordering Trisporal (itraconazole; new order) when Prograf (tacrolimus; current order) is already on the patient's medication list. The screenshots presented to the respondent also include a single information sentence put above the alert, which contains the DDI database code, the evidence index, seriousness index, and the number of times the alert has been overridden in one month.

pharmacy review. Free text prescriptions do not generate drug safety alerts. The CPOE system cannot use clinical chemistry data or existing patient drug serum levels to either generate or suppress alerts. Medicatie/EVS® version 2.20 allows only for hospital-wide turning off alerts. The knowledge base for drug safety alerting in the system makes use of the national G-standard, which is updated monthly and can be customized according to local requirements.

Participants

All medical ward coordinators (specialists) in internal medicine and cardiology were included as participants, as well as all registered hospital pharmacists working in the front office of the hospital pharmacy. Other specialists and residents known to be active users of the program and willing to participate were included to create equal sample sizes of six respondents for each specialty (internal medicine, cardiology, surgery) and hospital pharmacy. In total, 18 physicians and 6 pharmacists were recruited for the study, without using financial or other incentives. Although hospital pharmacists do not receive drug safety alerts in real time themselves, but only view overridden alerts, they were included as they are generally responsible for CPOE implementation and drug safety, including checks on overrides and turning off alerts.

Data collection

The total number of overridden drug safety alerts was analyzed for 1 month (October 2005) in the general hospital of Erasmus MC. DDIs overridden more than 10 times per month were selected for further evaluation. Those DDIs without an alphanumeric code were excluded because seriousness was thought to be an important consideration in specialists' decisions whether to turn off [14]. The DDIs concerning drug administration time were excluded as well because it was proposed to direct these alerts to other people in the workflow [15]. As overriding may have different causes and reasons that cannot be detected from quantitative analysis [5], the study conducted qualitative interviews of prescribing physicians. Printed screenshots of the 24 remaining overridden DDI alerts were presented to the respondents, who were asked whether this DDI could be turned off, hospital-wide, without impairing patient safety. They were also asked to provide their reasons for this decision. Override rate, DDI name, database code and alphanumeric code were also shown to respondents (Figure 1). After they had assessed the DDI alerts, the respondents were then asked the same question again after being presented with the complete alert text (Figure 2). All interviews were conducted by the first author using an interview protocol. Interviews lasted 14 to 43 minutes and were audiotaped.

Analysis

Interviews were transcribed verbatim and analyzed. The number of alerts that respondents recommended to be turned off hospital-wide were counted and related to specialty, job status, and alert type. The number of decision changes due to the presentation of the complete alert text was calculated.

Every recommendation to turn off an alert was coded manually with one or two relevant keywords representing the main reason for the respondent's opinion (Table 1). These reasons were derived from items used for the classification of DDIs in the Dutch drug database [12], and referred to in literature [5]. To this list were added themes emerging from the interviews. Reasons for turning off an alert were analyzed as a whole, by drug safety alert, by specialty, and by function of the person recommending the action. Statistical tests were performed using

Tacrolimus and enzyme inhibitors (1465)

The serum level of tacrolimus may rise due to CYP3A4 inhibition, with possible nephrotoxicity as a result.
CYP3A4 inhibitors are danazol, diltiazem, felodipine, fluconazol, itraconazol, ketoconazol, nicardipine, nifedipine, verapamil. For claritromycin, erytromycin and voriconazole, see drug-drug interaction 5096. Serum level of tacrolimus will drop upon stopping the enzyme inhibitor.

Recommendation:
Replace the enzyme inhibitor with another drug, preferrably always in consult with the prescriber of tacrolimus. If the combination is prescribed, monitor the serum level of tacrolimus upon starting or stopping the enzyme inhibitor.

Mechanism:
Tacrolimus is mainly metabolized by CYP3A4. Enzyme inhibition by CYP3A4 in the liver and intestinal wall results in decreased liver metabolism of tacrolimus and increased bioavailability.

Figure 2 Translated example of a complete text of a drug-drug interaction
The boxed text can be observed at a glance; the rest of the alert text can only be read if it is scrolled down to the bottom.

SPSS version 15 (SPSS Inc., Chicago, IL). Correlation analysis was used to examine the strength and direction of linear relationships between variables. Spearman's Rank Order Correlation (rho) was used as a nonparametric test to calculate the strength of the relationship.

RESULTS

A total of 3,089 drug safety alert overrides occurred in October 2005. This comprised 1,963 DDIs (64%), 684 overdosage alerts (22%), and 442 duplicate order alerts (14%). In the DDI category, a total of 86 different individual alerts were overridden. Of those, 32 alerts occurred more than 10 times. Eight alerts were excluded because their relevance had not been assessed completely, and they had not yet been assigned an alphanumeric code, or because the interaction referred to administration time. The study used the remaining 24 individual alerts for its assessments (Table 2). These alerts accounted for 72% of all overridden DDI alerts (1,413 of 1,963). High-level alerts (E/F 25%), medium-level alerts (C/D 54%) and low-level alerts (A/B 21%) were present.

Table 1 Response analysis: reasons and number of times mentioned

Each alert assessment resulted in one to two main reasons per respondent for the opinion whether to turn off.

Reason	Explanation of reason	Number of times reasons mentioned by respondents						
		Per specialty				Overall	Resulting in turning on or off	
		Internal medicine	Cardiology	Surgery	Hospital pharmacy		On	Off
Seriousness[12]	DDI is mentioned to be serious, not serious, clinically relevant or irrelevant; the letter of the alphanumeric code is mentioned.	39	30	20	67	156	115	41
Evidence[12]	The evidence of the DDI is mentioned or the number of the alphanumeric code.	7	0	1	4	12	8	4
Risk patients[12]	Risk factors making the DDI relevant are mentioned.	3	4	0	1	8	8	0
Incidence[12]	The incidence of adverse events due to the DDI is mentioned.	8	6	3	0	17	5	12
No action[12]	The respondents mention the alert does not need any action or that they never perform any action.	7	9	11	6	33	0	33
Text [12]	The information in the alert text is mentioned (recommendations to adjust doses, to measure serum levels, monitor patient parameters, or prescribe alternative drugs).	15	24	29	27	95	95	0
Number[5]	The quantity or number of alerts (generated or overridden) is mentioned.	3	5	4	10	22	15	7
Knowledge[5]	The fact that the alert is known or unknown is mentioned.	72	40	27	20	161	104	57
Specialty[5]	The fact that only specialists are prescribing a specific drug or the combination of drugs is mentioned.	1	11	8	4	24	0	24
Urgency[5]	The rapidity of the adverse effect is mentioned.	3	2	0	8	13	4	9
Monitoring[5]	The fact that effects are monitored or serum levels measured is mentioned.	7	12	6	22	47	0	47
Intentional	The fact that the drugs are intentionally combined because of a desired effect of the DDI or the fact that they are generally combined for other reasons is mentioned	11	9	1	17	38	0	38
Hospital-wide	The fact that the drugs are prescribed by two or more different specialties is mentioned	2	14	0	9	25	25	0

The 24 respondents included 4 specialists and 2 residents in internal medicine and cardiology, 4 registered hospital pharmacists, and 2 residents in hospital pharmacy. For surgery, only 2 specialists were available for interviews because attending surgeons never prescribe on inpatient wards and only supervise residents. Therefore, 2 specialists and 4 (final year) residents were recruited. The 24 respondents together made 576 assessments.

Quantitative analysis of recommendations to turn off alerts

The number of respondents agreeing that a given alert could be turned off hospital-wide is presented in Table 2. There were no alerts that all clinicians agreed could be turned off safely. However, a significant positive correlation of 0.44 (α=0.05) was found between the number of overridden alerts and the number of physicians recommending alerts to be turned off. This suggests that an increase of alert overrides increases the number of physicians advising to turn off alerts. No correlation was found between the level of seriousness and the number of respondents agreeing to turn off alerts hospital-wide. For three alerts, at least 50% of the 24 respondents recommended suppression hospital-wide.

Six clinicians (four for surgery and two for cardiology) did not want to turn off any alerts. Specialists agreed four alerts should not be turned off hospital-wide, whereas several residents thought these could be turned off safely. Hospital pharmacists always made their decisions for the entire hospital, but many physicians reported that they could not make this decision for colleagues outside their specialty. Several decisions to turn off alerts could only be made for their own specialty (19%, 12%, and 94% of the decisions of internists, cardiologists, and surgeons, respectively), whereas others were made for the entire hospital (81%, 88%, 6%, respectively).

Specialties differed in the number of alerts they thought could be turned off hospital-wide. Internal medicine recommended more alerts be turned off than cardiology and cardiology more than surgery. Internists agreed on turning off four alerts for their own specialty, which would result in a mean reduction of overridden alerts of 19% for their specialty. The residents asked for turning off for their specialty more often than the specialists. Eight residents made 83 requests for turning off, whereas 10 specialists asked 76 times.

Five times, respondents could not make a decision whether to turn off an alert with the limited information on the printed screenshot, but they were able to do so with the complete text presented in the second part of the study. The request to turn off an alert changed in 14 assessments after presentation of the complete text (2.4% of total). Hospital pharmacists changed their opinion more often (7 times) than internists (3 times), cardiologists (0), and surgeons (4). In 63 assessments (11%), respondents spontaneously commented negatively on the length, content, and sequence of the complete text presented.

Qualitative analysis of recommendations to turn off alerts

Qualitative analysis showed that at the beginning of their interviews, three respondents mentioned a reason for not turning off any alerts hospital-wide. A cardiologist said that the question

Table 2 Alerts, number of respondents agreeing to turn off the alert, and reason most often mentioned.
The DDIs are ordered according to the seriousness index.

DDI database code	DDI name	Seriousness index	Evidence index	Number of alert overrides in one month	Number of clinicians agreeing to turn off alerts					Reason most often mentioned
					Int (n=6)	Card (n=6)	Surg (n=6)	Pharm (n=6)	Total (n=24)	
1066	Potassium and potassium-saving diuretics	F	3	41	4	1	0	6	11 (46%)	Knowledge (7)
0035	ACE inhibitors and potassium-saving diuretics	F	2	112	1	2	0	6	9 (38%)	Knowledge (10)
0280	Beta-blockers and verapamil/diltiazem	E	3	12	1	2	1	3	7 (29%)	Knowledge (6) Intentional (6)
5096	QT interval prolonging drugs erythromycin/ clarithromycin/voriconazole	E	3	10	1	0	0	0	1 (4%)	Seriousness (11)
3395	Statins (simvastatin/atorvastatin) and verapamil/ diltiazem	E	3	10	0	1	0	0	1 (4%)	Text (9)
5088	QT interval prolonging drugs and QT interval prolonging drugs (except erythromycin, clarithromycin, voriconazole)	E	1	154	0	0	0	0	0 (0%)	Seriousness (12)
0531	Coumarins and amiodarone/propafenone	D	3	47	3	4	0	5	12 (50%)	Monitoring (12)
0299	Nonselective beta-blockers and insulin	D	3	18	3	4	0	4	11 (46%)	Knowledge (7)
0019	ACE inhibitors and diuretics	D	3	312	2	2	0	3	7 (29%)	Knowledge (6) Intentional (6)
3921	Haloperidol and enzyme inductors	D	3	14	1	0	1	3	5 (21%)	Knowledge (7)
1155	Diuretics and NSAIDs	D	3	41	2	0	0	2	4 (17%)	Seriousness (14)
0027	ACE inhibitors and NSAIDs	D	3	30	1	0	0	2	3 (13%)	Seriousness (14)
0124	Digoxin and amiodarone	D	3	16	0	1	0	1	2 (8%)	Seriousness (9) Knowledge (9)
1465	Tacrolimus and enzyme inhibitors	D	3	27	0	0	0	0	0 (0%)	Seriousness (11)
3360	NSAIDs (except COX-2 inhibitors) and selective 5HT reuptake inhibitors/trazodone	C	4	15	0	0	1	1	2 (8%)	Knowledge (9)
0272	Beta-blockers and NSAIDs	C	3	37	5	3	0	4	12 (50%)	Knowledge (9)
2046	NSAIDs (except COX-2 inhibitors) and corticosteroids	C	3	83	2	1	1	2	6 (25%)	Knowledge (9)

Table 2 continued

DDI database code	DDI name	Seriousness index	Evidence index	Number of alert overrides in one month	Number of clinicians agreeing to turn off alerts					Reason most often mentioned
					Int (n=6)	Card (n=6)	Surg (n=6)	Pharm (n=6)	Total (n=24)	
0736	Coumarins and NSAIDs	C	3	29	2	1	0	2	5 (21%)	Knowledge (6)
0310	Nonselective beta-blockers and beta-adrenergic agonists	C	3	12	2	2	0	1	5 (21%)	Text (8)
0302	Selective beta-blockers and insulin	B	3	160	3	4	0	6	13 (54%)	Knowledge (9)
3964	Beta-blockers and oral hypoglycemic drugs	B	3	57	3	3	1	4	11 (46%)	Knowledge (8)
1228	AT receptor antagonists and diuretics	B	3	87	2	3	0	3	8 (33%)	Knowledge (5) Intentional (5)
0078	Alpha-blocking drugs (for benign prostate hyperplasia) and beta-blockers/calcium channel blockers	B	3	78	1	0	0	4	5 (21%)	Knowledge (8)
0345	Calcium channel blockers and CYP3A4 inhibitors	B	3	11	3	0	0	2	5 (21%)	Knowledge (10)
Total				1413	42	34	5	64	145	

( ) = number of respondents mentioning this reason.

5HT = serotonin; ACE = angiotensin-converting enzyme; AT= angiotensin; Card = cardiology; COX-2 = cyclooxygenase-2; CYP3A4 = cytochrome P450 3A4; DDI = drug-drug interaction; Int = Internal medicine; NSAID = nonsteroidal anti-inflammatory drug; Pharm = hospital pharmacy; Surg= surgery.

about hospital-wide turning off was useless and bad because residents early in their training do not have the appropriate knowledge. The surgeons said that the drug and DDI knowledge of residents and specialists in surgery was too low and therefore every DDI should be shown. These three respondents were excluded from further qualitative analysis of reasons because they did not mention reasons for single alerts. One internist was reserved about alert suppression and favored frequent alerting, saying: 'I prefer having a bit too many alerts than too few'.

Reasons for suppression of alerts and the number of times they were mentioned are presented in Table 1. Two new themes emerged in the interviews. The first theme was about drugs that are combined intentionally by the same specialist because the effect of the DDI is advantageous in a specific patient group, whereas the combination might cause harm in others (e.g., intended bradycardia due to beta-blockers combined with verapamil or diltiazem, prescribed by a cardiologist). The second theme that emerged was a combination of drugs that are generally prescribed individually within each of two or more specialties (e.g., alpha-blockers for benign prostate hyperplasia by urology and beta-blockers by internal medicine) that might cause problems if the alert is suppressed. The internist may not focus on the possible harmful effects of combination of a known beta-blocker with a rather unknown alpha-blocking drug the internist never prescribes.

'Knowledge' and 'seriousness' were the most frequently mentioned reasons for not turning off alerts, followed by 'text'. Reasons used for the classification and presentation of DDIs in the G-standard (seriousness, evidence, risk factors, incidence, action, text) were mentioned about as often as more context-specific reasons (knowledge, intentional, monitoring). Risk factors, incidence and evidence were not mentioned very often, nor were the number of alerts.

Thirty-three times (6%) respondents mentioned that alerts were not acted upon or did not need any action, whereas all alerts were categorized as yes/yes-interactions in the Dutch drug database.

Results viewed per alert

Respondents rated four alerts that could result in increased risk of Torsades de Pointes, myopathy, and nephrotoxicity as unknown and serious, with adverse effect preventable by following the recommendation given, and recommended unanimously that these 4 alerts should not be turned off. The interaction alerts due to QT-interval prolongation and liver enzyme inhibition were not directly deducible from the pharmacological group of drugs and therefore perceived as largely unknown and useful.

At least 50% of the respondents stated that three specific alerts could be suppressed hospital-wide, because related effects were either monitored regularly by measuring the international normalized ratio, well known and not serious, or irrelevant (in the case of short-term treatment with nonsteroidal anti-inflammatory drugs). Respondents very often characterized frequently overridden sequence-dependent alerts as false positives, for example, when a diuretic was added to therapy with an angiotensin-converting enzyme inhibitor or to an

angiotensin receptor antagonist. Internists (and cardiologists also) frequently prescribed such combinations, were aware of these alerts, and asked to turn them off. The drug combination of potassium-saving diuretics with potassium was said to be known, intentional, and always based on low potassium levels and therefore not useful. The low-level B-alerts were perceived as serious eight times (7%). On only one occasion was a high-level E-alert described as not serious.

Results viewed per specialty

Surgeons gave a lower average number of different reasons for alert suppression or retention (4.5) than did hospital pharmacists (8), internists (7.3), and cardiologists (8). Surgeons relatively often mentioned 'text' as a reason not to turn off and 'no action' as a reason to turn off alerts. Hospital pharmacists relatively often mentioned 'seriousness', 'number', 'monitoring', and 'intentional', whereas 'knowledge' was hardly considered. Internists very often mentioned 'knowledge' as a reason for suppression, whereas cardiologists referred more to 'specialty-specific' prescribing. Physicians generally included their own experience in their considerations. Internists and cardiologists often asked to turn off the DDIs having to do with the serum potassium level because these levels are measured routinely for inpatients. Surgeons admitted they do not regularly measure these levels and prefer these high-level F-alerts to be shown.

Results viewed by job status (residents versus specialists)

The number of alerts recommended to be suppressed per respondent was higher for residents than for specialists; this difference was highest for surgeons. Residents more often mentioned 'no action', 'only prescribed by specialists', and 'low incidence' as reasons for alert suppression than did specialists. One surgical resident did not understand the text of the sequence-dependent alerts well, considered the administration of drugs was out of the control of physicians, and thought these alerts therefore irrelevant. However, the alert related problems arising when the patient had previously been using a diuretic for a while.

DISCUSSION

This study attempted to identify opportunities to safely turn off (suppress) drug alerts hospital-wide. Nevertheless, the respondents rating alerts across specialties as well as within one specialty differed substantially in their recommendations and reasons for suppression of drug safety alerts, even when only medical specialties were taken into account. The same sorts of differences occurred for residents and specialists. Opinions on whether to suppress alerts changed minimally when more information was presented. Hospital-wide suppression was deemed not feasible.

Unexpected study results

The study results surprised the authors in several regards. First, one-quarter of respondents (all physicians) recommended not turning off any alerts hospital-wide, either because the alerts did not bother them, or because they feared that a perceived lack of knowledge among residents and surgeons would lead to errors that alerts could prevent. This surprised the investigators because a major motivation for the study was the high frequency of physicians' complaints about DDI alert overload prior to the study. Differences in preferences and reasoning were observed between as well as within specialties. These results suggest to the investigators that alert presentation might improve if it is customized to specialty and job status. This is in line with previous recommendations in literature [14].

Second, no positive correlation could be observed between the nationally determined level of DDI seriousness ratings and the number of respondents stating that the alert should be suppressed. Seriousness was very often mentioned as an important consideration in the decision about whether to suppress an alert, but several times the respondents' perceived seriousness did not correspond with the national seriousness index. Physicians may perceive alerts as not serious because frequent monitoring in the hospital setting provides direct feedback about whether harm is imminent. However, the ability to monitor serum levels or patient parameters was only mentioned 47 times (8%) as an important reason to suppress an alert, whereas the majority of the alerts have effects that can be assessed by measuring serum levels, heart rate and rhythm, or blood pressure.

Third, respondents cited the number of alerts being overridden only 22 times (4%) as an important consideration for alert suppression, and the literature supports that other factors are more important for the perceived usefulness of alerts [14]. However, the current study observed a positive correlation between the number of overrides for a given alert and the number of physicians recommending that the specific alert be turned off. A possible explanation for this correlation is that frequently shown alerts resulted in a learning effect [16] and were characterized by respondents as 'alert well known' instead of citing the number of alerts overridden or generated.

Fourth, presentation of the complete texts rarely resulted in opinion changes, but spontaneously prompted negative comments on text content, sequence, and length. It is said that drug safety alerts should not be lengthy, but clear and concise to be helpful, with links to supporting evidence [11]. Users do not review alert texts prior to inclusion in the Dutch drug database, although their comments are welcomed and sometimes acted on. The investigators advise having clinician-users review potential DDI alert texts prior to introducing them into practice.

Error management

Several times, physicians did not rate seriousness of an alert correctly (i.e., according to the national categorization). They rated some alerts as not serious (and thus candidates for suppression) when they had never seen the adverse reactions, or when the physicians generally

had not taken any actions upon presentation. Furthermore they did not consider risk factors. These results suggest that physicians cannot always envisage all potential adverse events of drug combinations and that structural assessments, as well as better education of the users about the alphanumeric codes, risk factors, and DDI incidence rates would probably help.

This study shows that many physicians used considerations that are questionable from a safety perspective, like 'effects intended', 'only prescribed by specialists', 'no action needed', or 'alert well known', and that they hardly considered risk factors. When a drug combination is intentionally prescribed by physicians in one specialty, it does not imply that other specialties will prescribe it safely (or that they will never prescribe it), so such alerts cannot be safely turned off hospital-wide. Many residents mentioned they would never act on an alert ('no action') and it could therefore be turned off. This reason is given far less frequently by specialists and is problematic from a safety perspective, but is in line with the observation that those who need alerts most would turn them off [11]. Lack of clinician end-user knowledge can be a good reason not to turn off alerts. It is questionable as a reason for knowledge-specific or specialty-specific alert suppression [14], because a recent British study indicated that 57% of prescribing errors were due to incorrectly executing an appropriate plan, because clinicians were busy, or had been interrupted during routine tasks [17,18]. Lack of attention, distraction, and forgetfulness, rather than a lack of knowledge, have been cited as frequent causes of errors [19]. Therefore, even turning off alerts for experts would carry some safety concerns.

Alerts in Medicatie/EVS® appear as pop-ups [13]. Literature suggests that these intrusive alerts should only be used for the most severe clinical indications [20], when the situation requires remedial action before the prescription becomes complete [3]. Nonintrusive presentations can take the form of sidebars [21] or as nonintrusive text messages on the ordering screen [3,22]. The DDIs in this study all have been categorized as interacting and requiring action (yes/yes DDIs) [12]. It is not clear whether nonintrusive alerts would induce alert fatigue or not, and whether they would result in the preferred action required to prevent adverse events. Further research must occur to assess the cognitive burden of various forms of alerts on the user. For example, it might be the case that when yes/yes DDI alerts whose effects can be measured via serum levels are turned off, or are shown nonintrusively, the CPOE system should also incorporate clinical rules that not only check if serum levels are within the therapeutic window, but also if these levels have been ordered and measured.

Strengths and weaknesses of the study

The current study had several unique features. Whereas other studies have focused on turning off alerts of a commercial knowledge base after iterative consensus based discussions by an expert panel [2,3], this study took the consensus based knowledge base [12] as a starting point for further customization. Other studies analyzed override reasons for specific patients [3,6,23], whereas this study focused on considerations for hospital-wide alert suppression, and included assessment of perceived usefulness of alerts for physicians. The qualitative part of the study

design helped to identify new reasons for alert suppression, and initiated a dialogue about unclear answers. The interviews in this study were performed one-to-one to prevent individual opinions changing under the influence of a group of respondents. The study included six experts per specialty and revealed within-specialty differences in recommendations and reasons. By contrast, expert panels generally include a smaller number of experts per specialty. This study revealed many unexpected results and gave an insight into what direction future research on alert suppression might follow; specifically, investigation of safe mechanisms for specialty- or knowledge-specific alert suppression and investigation of how to optimally word the alert text.

The current study also had limitations. The study examined only 24 individual DDI alerts, and sought opinions from only three medical subspecialties. Including the pharmacists, the study obtained 576 person-alert assessments. The alerts accounted for the majority of overrides in an October 2005 sample of hospital activity (24 alerts accounted for 72% of all overrides and 60% of the alerts were overridden by the 3 specialties). Overriding was nearly equally common among the three medical specialties: 22%, 17%, and 20% for internal medicine, cardiology, and surgery respondents, respectively. In a March 2006 follow-up, the selected alerts and medical specialties still accounted for 67% and 58% of the overrides, respectively. The percentage of overridden DDI alerts compared to the total number of overridden alerts was relatively constant (64 and 61% for October 2005 and March 2006, respectively). The majority of the 24 selected alerts (58%) are also frequently encountered in Dutch community pharmacies [24].

More specialists than residents were included in this study because in our opinion the responsibility for turning off alerts for the entire hospital cannot put on the shoulders of residents; specialists should make this decision. However, residents prescribe more, are more likely to suffer from alert fatigue, and perhaps are therefore more willing to turn off alerts than specialists. To eliminate a learning effect as much as possible, only final-year residents were included in this study [25].

Only respondents willing to participate were recruited, which may have resulted in selection bias. The respondents, however, represented a large variety of opinions and arguments. It is therefore unlikely that inclusion of other respondents would have resulted in different conclusions.

CONCLUSIONS

Overly inclusive drug databases for CPOE drug safety alerting can cause alert fatigue and can impair patient safety. Turning off (suppressing) alerts is a potential mechanism to reduce alert fatigue, and may be safe for alerts irrelevant in certain specific clinical contexts. Future research must verify these impressions. The drug database used in Dutch CPOEs was not overly inclusive,

but investigators observed before, during, and after the study that many physicians complained about too many alerts and asked for selective suppression of alerts.

This study attempted to identify opportunities to turn off DDIs hospital-wide safely, but the results suggest that this may not be feasible. None of the study participants unanimously agreed that hospital-wide suppression of a specific alert could occur safely. Within one hospital, knowledge about DDIs and their sequelae, and routine monitoring practices differed considerably across specialties, and also between specialists and residents. These observations suggest that alert suppression might be studied and implemented in a specialty-specific or knowledge-specific manner. Furthermore, in their recommendations to turn off DDI alerts, respondents frequently cited reasons that are questionable from a safety perspective. The national seriousness index for an alert and the number of clinicians recommending its suppression were not correlated. In contrast, the study found a positive correlation between the number of alerts overridden and the number of clinicians recommending the suppression of the alert. The latter finding should be examined in a larger-scale study.

The investigators concluded that hospital-wide DDI alert suppression is not feasible. Future research should examine the potential effectiveness of sequence-specific DDI alerting, of methods to optimize alert texts, approaches for knowledge-specific and specialty-specific alert suppression (or alternatively, using nonintrusive alert presentation), and methods to provide safety during alert suppression, such as implementing concomitant clinical rules that check whether serum levels or patient parameters are indeed measured and stay within limits.

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Chapter 3.2

Addition of level of seriousness to drug safety alert texts: better informed but increased overriding

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Chapter 3.3

Time-dependent drug-drug interaction alerts in CPOE: software hampers drug administration error reduction

Heleen van der Sijs, Laureen Lammers, Annemieke van den Tweel,
Jos Aarts, Marc Berg, Arnold Vulto, Teun van Gelder

ABSTRACT

Time-dependent drug-drug interactions (TDDIs) are drug combinations that result in a decreased drug effect due to co-administration, which can be prevented by administering the drugs separated by an appropriate time interval. Our objective was to reduce drug administration errors due to overridden TDDIs in a computerized physician order entry (CPOE) system. In four periods divided over two studies, logged TDDIs were investigated by reviewing the time intervals prescribed in the CPOE and recorded on the patient chart. The first study showed significant drug administration error reduction from 56.4% to 36.2%, whereas the second study was not successful (46.7% and 45.2%). Despite interventions, drug administration errors still occurred in more than one-third of cases and prescribing errors in 79-87%. Probably, the low specificity, unclear information content of the alerts and the software not allowing safe and efficient TDDI alert handling hampered correct prescribing, resulting in insufficient reduction in drug administration errors.

INTRODUCTION

Computerized physician order entry (CPOE) systems frequently include integrated decision support components, which can reduce errors and improve patient safety [1-6]. Drug safety alerts are designed to prevent medication errors but are often not read, misinterpreted or handled incorrectly, impairing their potential effect on patient safety [7].

Time-dependent drug-drug interactions (time interactions, TDDIs) are drug-drug interactions (DDIs) resulting in a decreased drug effect due to co-administration, which can be prevented by administering the drugs separated by an appropriate time interval (generally 2-4 hours). In TDDIs, the mechanisms by which absorption is reduced are complex formation (tetracyclines and divalent ions), increased pH (iron and antacids) or decreased enterohepatic circulation (mycophenolate mofetil and antacids). As drug administration is typically a nursing task, it was hypothesized that directing TDDI alerts to nurses could reduce the burden of drug safety alerts on physicians and decrease the number of drug administration errors [7,8].

The aim of this study was to reduce drug administration errors due to TDDIs by educating nurses and physicians and by reducing the burden of TDDI alerts.

Questions posed by this study are:

1. How often are drug combinations resulting in TDDIs prescribed and administered incorrectly?
2. What is the effect of educating physicians and nurses about TDDIs and drug administration errors? (short and long term)
3. Can the burden of TDDI alerts be decreased by directing TDDI alerts to other people in the workflow, such as nurses (or pharmacy technicians)?

METHODS

The Erasmus MC in Rotterdam, the Netherlands, is a 1,237 bed academic medical center on 3 sites that started using CPOE in December 2001. Since March 2005 all inpatient wards, intensive care units excluded, have used the CPOE system Medicatie/EVS® (iSOFT, Leiden, the Netherlands) [7,9]. As nurses are not legally allowed to prescribe drugs, physicians (and midwives) exclusively enter medication orders. During order entry physicians can select dosage regimens (e.g., thrice daily) that are translated to the corresponding drug administration times on the ward and these administration times can be adjusted when desired. Printed order labels are stuck on paper charts, nurses write the intended drug administration times next to the prescribed times of the order labels, and sign for drug administration.

Drug safety alerts and the corresponding alert texts in the CPOE are based on the national Dutch drug database (G-standard) [10] and are presented intrusively (Figure 1). When a TDDI alert is presented physicians are supposed to adjust drug administration times or to place a remark in the order that the drugs should be administered separately, with at least the required

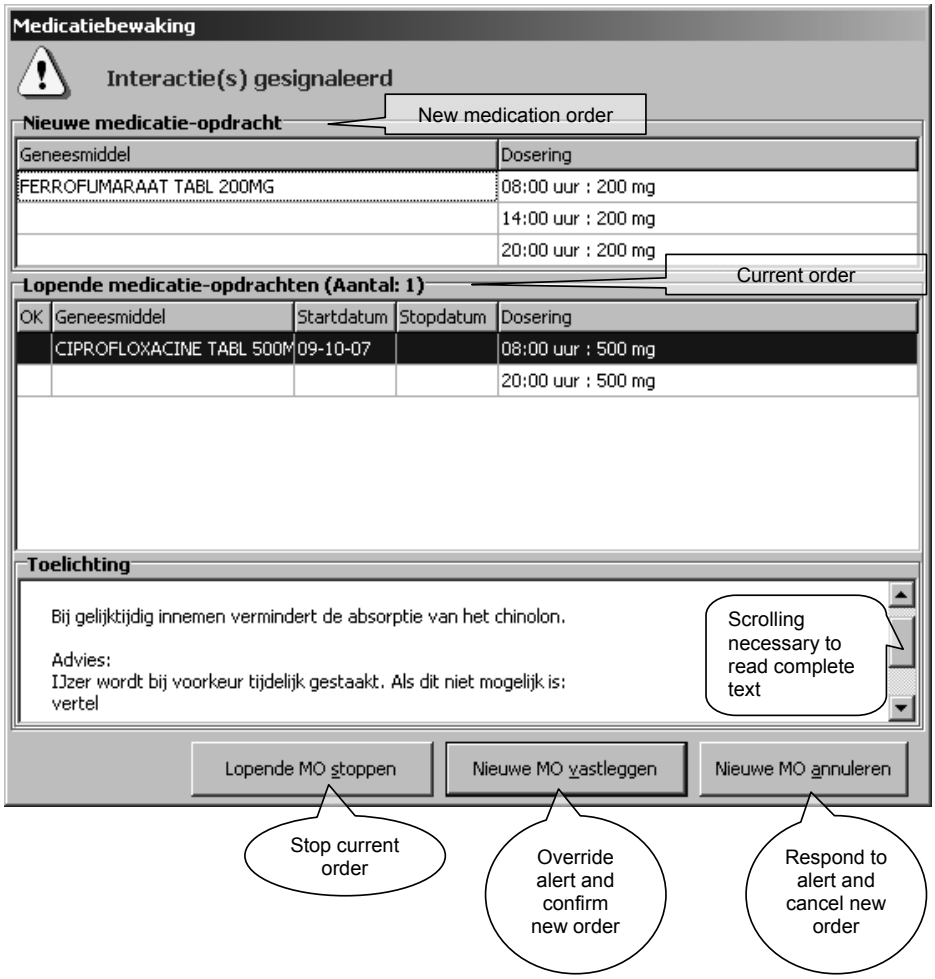

Figure 1 Time-dependent drug-drug interaction alert quinolones and iron
DDI alert presented to a physician ordering ferrofumarate when ciprofloxacin is already on the patient's medication list. Only part of the alert text (the boxed text below) is shown without scrolling.
Complete (translated) alert text:

Taking these drugs concomitantly decreases quinolone absorption. Recommendation: Preferably stop iron temporarily. If this is not possible: tell

the patient that the quinolone should be taken at least 2 hours BEFORE the iron.

time interval given in the alert text. TDDI alerts are generated irrespective of the drug administration times entered, which results in false positive alerts if time intervals are prescribed correctly.

We analyzed all TDDI alerts logged in Erasmus MC's 800-bed general hospital (Center Location) in 4 periods divided over 2 studies. The study design is presented in Figure 2. In study 1, after a 24-day baseline period on 8 internal medicine wards in October 2004, feedback about

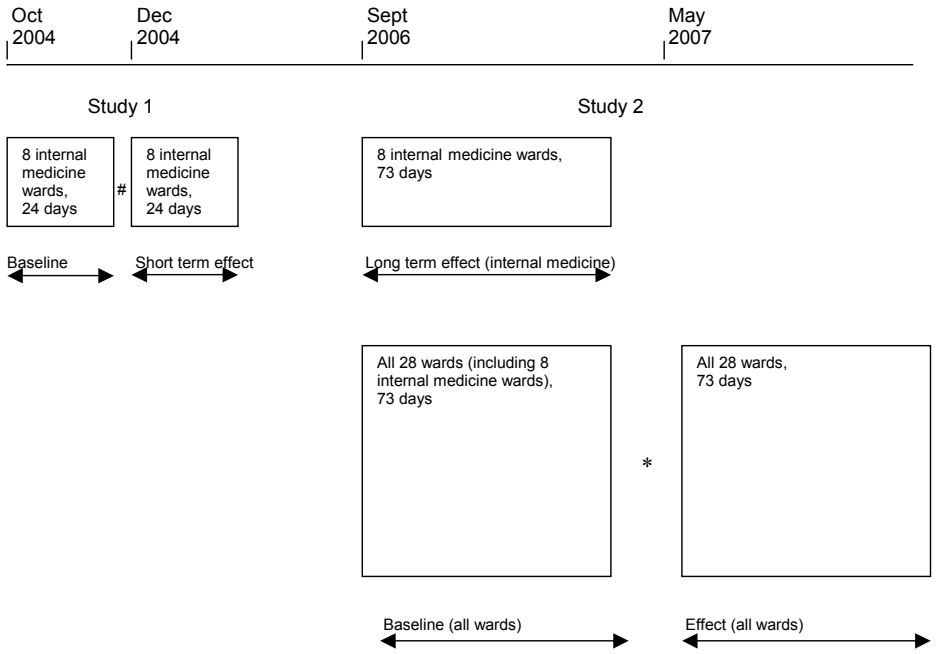

Figure 2 Study design
education of physicians and nurses, a table with TDDIs and their required time intervals made available, followed by daily feedback by the clinical pharmacologist
* discussion of results of the baseline period with head nurse and medical coordinator, followed by feedback by pharmacy technicians

drug administration errors was given to all nurses and physicians and a table with TDDIs and their required time intervals was made available. In the 24-day effect period the clinical pharmacologist communicated every incorrect time interval on the patient chart personally to the attending nurse and physician; monitoring of TDDI handling continued.

Study 2: the 73-day baseline period ran from September to November 2006 on all 28 wards of the general hospital, including the wards of the first study. The pharmacist then presented baseline results to the head nurse and the medical coordinator and suggested that nursing (or pharmacy) staff adjust administration times if TDDIs were encountered. A TDDI table was not made available to the wards new to the study. In the 73-day effect period from May to July 2007 pharmacy technicians gave feedback to nurses about incorrect time intervals and asked the nurses to inform the prescribing physician. During this period the number of incorrectly handled TDDIs was again monitored.

A correct time interval was defined as a time interval that matched that given in the alert. For all TDDIs logged the prescriptions were checked for correct time interval prescription or appropriate comment. Actual written administration times on the patient charts on the ward were checked against the recommended time interval. The TDDI was categorized as 'unable to

be evaluated' if the patient was discharged, administration was under the patient's control, the order had been stopped already or if administration times were unclear. Statistical analysis was performed with the Chi-square test on all TDDIs that could be evaluated.

RESULTS

During the four study periods a total of 1,031 TDDI alerts were logged of which 749 (73%) could be evaluated. Sixty percent were due to the combination of any drug with calcium (of which half was due to the combination of bisphosphonates with calcium) and about 30% concerned antibiotics (quinolones and tetracyclines). In 17% of all TDDI alerts that could be evaluated, a TDDI alert was generated despite a correctly prescribed time interval (false positive alert).

One month after the study 1 intervention, the percentage of drug combinations administered incorrectly had reduced from 56.4% to 36.2% [11] and two years later this was still 38.9%,

Table 1 Number of TDDI alerts and handling internal medicine before and after intervention of verbal and written education given in November 2004

	Baseline (24 days; Oct 2004)		Short term effect (24 days; Dec 2004)		P-value	Long term effect (73 days; Sept-Nov 2006)		P value
	Number	Percentage	Number	Percentage		Number	Percentage	
TDDI alerts	61		66			218		
TDDI alerts/day	2.5		2.8			3.0		
TDDIs that could be evaluated	55	90.2	58	87.9		193	88.5	
Prescribed incorrectly	54	98.2	46	79.3	<0.02	167	86.5	<0.02
Administered incorrectly	31	56.4	21	36.2	<0.05	75	38.9	<0.05

without any feedback having been given in the meantime (Table1). Figures for prescribing errors remained very high (79.3% and 86.5%). Nurses were preventing many drug administration errors by adjusting incorrectly prescribed administration times, but still more than one-third of TDDIs resulted in an administration error. The table with the required time intervals still appeared to be present on many wards on the wall of the medication room.

In the baseline period of the second study, incorrect time intervals were communicated to the nurses. However, the percentages of incorrectly administered drug combinations per week, 44%, 31%, 39% and 40% respectively in the first 4 weeks did not show a learning effect. The percentage administration errors on wards given feedback earlier was significantly lower (23.6%) than on wards not included in the first study (54.4%). This was not due to physicians prescribing time intervals correctly (14.5% versus 17.7%), but to corrective action by nurses.

Results of the baseline measurement and suggestions for TDDI handling by nurses were discussed on individual wards with the medical coordinator and head nurse. Directing TDDI alerts

to nurses or pharmacy personnel was not accepted and both agreed that physicians should prescribe correctly to prevent administration errors. The medical coordinators would inform their staff about the TDDI medication errors. No significant reduction in drug administration errors (46.7% to 45.2%) or prescribing errors (83.2% to 81.1%) could be observed despite pharmacy technician feedback on incorrect time intervals (Table 2). Nurses said they would inform the physician about incorrect time intervals, but pharmacy requests for administration time adjustments more often resulted in correct time intervals on the patient chart (86%) than in the prescribed order (10%).

Table 2 Number of TDDI alerts and handling all wards before and after discussing TDDI medication errors with head nurse and medical coordinator

	Baseline (73 days; Sept-Nov 2006)		Effect (73 days; May-July 2007)		P-value
	Number	Percentage	Number	Percentage	
TDDI alerts	454		450		
TDDI alerts/day	6.2		6.2		
TDDIs that could be evaluated	364	80.5	272	60.4	
Prescribed incorrectly	303	83.2	218	81.1	>0.05 NS
Administered incorrectly	170	46.7	123	45.2	>0.05 NS

DISCUSSION

This study revealed several unexpected results. Firstly, the number of TDDI prescribing and administration errors was very high and could not be reduced to an acceptable level.

Secondly, the first intervention with verbal education, written information and 23 days of intensive feedback had a long-lasting effect. In the second study, nurses were preventing many administration errors using the information leaflet with required time intervals that had been made available 2 years earlier. The information leaflet was often present in the medication room where nurses stick order labels on paper charts and write down the drug administration times.

Thirdly, formal adjustment of TDDI time intervals by nurses was not accepted, although these adjustments were common practice. The reason for this was not asked in the interviews, but the following assumptions can be made:1) TDDIs were not well known because of the low frequency of 6.2 per day over 28 wards. 2) Because administration errors were often corrected after pharmacy requests, adverse events did not occur often. Therefore these alerts perhaps were not perceived as serious enough to justify a formal responsibility shift from physicians towards nurses.

Fourthly, study 1 was effective and study 2 ineffective. The differences between the studies were fourfold:

1) In study 2 no education was given by pharmacy personnel, just a discussion was held with the head nurse and medical coordinator. It was not checked whether the medical coordinators indeed informed their staff.
2) No written information was made available to the new wards. Perhaps the leaflet with appropriate time intervals is required to enable nurses to prevent drug administration errors.
3) Feedback was given by pharmacy technicians instead of the clinical pharmacologist and probably did not reach the physician. If nurses did not communicate to physicians their administration time adjustments as corrections of prescribing errors, physicians cannot be expected to learn.
4) More surgical wards (with less pharmacotherapy-minded caregivers and fewer TDDIs) were included.

Error management

Incorrectly prescribed combinations (79%-98%), due to erroneous TDDI overriding, were an important cause of administration errors. This finding may imply that alert fatigue, caused by error-producing conditions such as low specificity, unclear information given by the alert, and the software not allowing safe and efficient alert handling, played a role [7]. Therefore, the process of TDDI alert handling was studied in more detail.

TDDI alerts were false positive in 17% of cases, generated though the time intervals were prescribed correctly. At present, none of the Dutch CPOEs has functionality to prevent false positive TDDI alerts, perhaps because the Dutch drug database lacks time indications; it would be worthwhile to develop them to improve specificity.

Requirements for useful information from drug safety alert texts include conciseness, non-ambiguity, clear level of seriousness, and presentation of an alternative action [7]. The most relevant part of the alert text recommendation (quinolone has to be taken at least 2 hours before iron) can only be read if it is scrolled down. The text is not unambiguous as it prompts 'tell the patient' rather than being customized to the hospital setting, where nurses administer drugs. The seriousness of the effect of overriding the alert is not clearly indicated in the text. The alternative action of adjusting administration times is proposed only as a second option (after stopping iron temporarily). The first sentence should recommend adjusting administration times to the required time interval; it would be worthwhile to investigate whether this alert adjustment results in less errors.

Handling of the TDDI alerts by the software appeared to be inefficient and error prone. In the CPOE three options are provided for handling the alert (Figure 1): 1) stopping a current order, 2) overriding the alert and confirming a new order and, 3) canceling a new order, whereas the preferred option to adjust the new order is absent. The order has to be canceled and newly prescribed, or confirmed but adjusted afterwards. The software is not helpful and may contribute to error generation [7]. Addition of a 'adjust order' button is recommended for safe and efficient

handling by the software, although future studies should investigate whether this indeed is less error prone.

After studying the whole process of prescribing and administering drugs, we postulate the following as an explanation for the unexpected study findings: low alert specificity, (un)-availability of clear information at the time of decision-making, (in)efficiency in responding to incorrect time intervals, and lack of clear responsibilities. The CPOE generates many false positive TDDI alerts, which may provoke alert fatigue, important alerts being ignored along with unimportant ones. In TDDI alert recommendations, the relevant information is hidden and not tailored to the hospital setting, so the information needed is not effectively shown to the physician at the time of decison-making. Prescribing by physicians after TDDI alerts is inefficient and unsafe. Physicians will not learn about the TDDIs if relevant alert information is hidden and nurses do not give feedback. Nurses on internal medicine wards were able to use the information leaflet with required time intervals when deciding on appropriate drug administration times, whereas nurses on other wards were not. Nurses could efficiently adjust administration times by writing on the patient chart. As nurses generally administer (oral) drugs, residents may perceive the handling of these TDDIs as nurses' responsibility, although formalisation appeared not to be accepted. In US hospitals where nurses, medication administration record transcribers and/or pharmacists are responsible for drug administration times, the proposed workflow probably would be implemented easily.

Strengths and limitations

To our knowledge, the topic of TDDIs has not been previously evaluated. All TDDI drug combinations irrespective of the prescribed time interval were available for review and it was feasible to study prescribing and administration errors, as well as the effect of two interventions.

Chart review was used to reveal incorrect administration times. Disguised observation, the preferred method for investigating drug administration errors, is very time-consuming and appeared to be too inefficient to study the relatively small number of about 6 TDDIs per day over 28 wards. A drug administration study performed with disguised observation in the ICU showed that 22.3% of drugs were administered more than one hour later or earlier than intended [12]. If we assume 78% of the incorrect time intervals to be indeed incorrect, this is still more than one third of all TDDI drug combinations.

In the effect period of the second study 60% of the TDDIs could be evaluated as compared to more than 80% in the other study periods. This low percentage appeared to be due to the pharmacy technicians checking time intervals in the afternoon when many patients had been discharged already. Furthermore, administration times were not always written down clearly. In case of doubt, these TDDIs were categorized as TDDIs that could not be evaluated.

This study did not include the clinical and financial effects of incorrectly administered drug combinations. Most of the TDDIs encountered are categorized in the G-standard as medium level seriousness with an increased risk of failure of therapy for a serious, non-lethal disease

[13]. It is therefore likely that problems may arise due to drug administration at incorrect times. Several error-producing conditions appeared to be present in the software that should be eliminated to enable improvements on a patient level.

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Chapter 3.4

Clinically relevant QTc prolongation due to overridden drug-drug interaction alerts: a retrospective cohort study

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ABSTRACT

Aim: To investigate whether, in patients in whom drug-drug-interaction (DDI) alerts on QTc prolongation were overridden, the physician had requested an electrocardiogram (ECG), and if these ECGs showed clinically relevant QTc prolongation.

Methods: For all patients with overridden DDI alerts on QTc prolongation during 6 months, data on risk factors for QT prolongation, drug class and ECGs were collected from the medical record. Patients with ventricular pacemakers, patients treated on an outpatient basis, and patients using the low-risk combination of cotrimoxazole and tacrolimus were excluded. The magnitude of the effect on the QTc interval was calculated if ECGs before and after overriding were available. Changes of the QTc interval in these cases were compared with those of a control group using one QTc-prolonging drug.

Results: In 33% of all patients with overridden QTc alerts an ECG was recorded within 1 month. ECGs were more often recorded in patients with more risk factors for QTc prolongation and with more QTc overrides. ECGs before and after the QTc override were available in 29% of the patients. Thirty-one percent of patients in this group showed clinically relevant QTc prolongation with increased risk of Torsades de Pointes or ventricular arrhythmias. The average change in QTc interval was +31 ms for cases and –4 ms for controls.

Conclusion: Overriding the high-level DDI alerts on QTc prolongation rarely resulted in the preferred approach to subsequently record an ECG. If ECGs were recorded before and after QTc overrides, clinically relevant QTc prolongation was found in one-third of cases. ECG recording after overriding QTc alerts should be encouraged to prevent adverse events.

INTRODUCTION

Many cardiac and noncardiac drugs have effects on cardiac repolarization and can prolong the QTc interval on the electrocardiogram (ECG). The use of these drugs is associated with an increased risk of serious ventricular arrhythmias (e.g., Torsades de Pointes (TdP)) and sudden cardiac death [1-10]. The QTc interval can be used as a surrogate marker for the prediction of sudden cardiac death. Although this relationship is indirect [2,3], prolongation of the absolute QTc interval beyond 500 ms and/or an increase of >60 ms is regarded as indicative of an increased risk of TdP [1,2,6,10]. Many studies investigated the effects and risks of the use of a single QTc-prolonging drug [2,3,8,9]. However, hardly any literature is available on the risks of TdP if two or more QTc-prolonging drugs are combined.

Computerized physician order entry (CPOE) systems with integrated computerized clinical decision support often generate drug-drug interaction (DDI) alerts on QTc prolongation. These alerts are frequently overridden, and it is not clear how often an ECG showing acceptable QTc intervals justifies this overriding. The aim of this study was to investigate whether overridden DDI alerts on QTc prolongation result in ECG recording and in how many instances this reveals clinically relevant QTc prolongation.

The questions to be answered were:

1. How often do overridden DDI alerts on QTc prolongation result in ECG recording following the prescription?
2. Are there any differences in risk factors, alert numbers or ward type between patients with and without ECG recordings?
3. Which drug combinations do result in clinical relevant QTc prolongation and risk of TdP?
4. Is QTc prolongation after addition of QT-prolonging drug(s) more pronounced than upon continuation of one QT-prolonging drug?

BACKGROUND

The QT interval on the surface ECG is measured from the beginning of the QRS complex to the end of the T wave and varies with heart rate. Therefore, the QT interval is generally corrected for heart rate, resulting in the QTc interval. Bazett's formula, which is often used for the calculation of the QTc interval, divides the QT interval by the square root of the RR interval ($QTc = QT/\sqrt{RR}$). Besides congenital long QT syndrome, many noncongenital factors may predispose to QT prolongation and higher risk of TdP, such as older age, female gender, cardiovascular disease (left ventricular hypertrophy, low left ventricular ejection fraction, ischaemia), bradycardia and electrolyte disturbances (hypokalaemia and hypomagnesaemia) [6]. Furthermore, several drugs may result in QTc prolongation by blocking potassium currents and/or by pharmacokinetically increasing serum levels of these drugs by DDIs reducing cytochrome P450 activity. Higher

doses and renal failure may also result in higher serum levels of these drugs and consequently in QTc prolongation [6].

QTc prolongation may predispose to ventricular arrhythmias, which may be fatal, but a linear relationship between QTc prolongation and risk of TdP is absent. However, a patient with a QTc interval >500 ms is regarded as at risk for TdP [2]. Of patients with TdP on QTc-prolonging drugs, 5-10% appear to have a subclinical form of the long QT syndrome [2], but for the majority of patients with TdP this is not the case. The relationship between potassium current blocking effect and TdP is not clear-cut either. Amiodarone blocks potassium currents and often prolongs the QT interval beyond 500 ms, but rarely causes TdP [2].

The G-standard is the Dutch national drug database and contains drug (safety) information for all drugs registered in the Netherlands, including DDIs [11]. All CPOEs in the Netherlands make use of this G-standard, which has included DDI alerts on QTc prolongation since March 2005. All drugs with clinical evidence of TdP (lists D and E of De Ponti [3,7]) were generating this alert, as well as all class Ia and III antiarrhythmics. The standardized alert text from the G-standard for DDIs on QTc prolongation is very long and consists of a summary of the effects of the combination, a recommendation about what to do, risk factors for a prolonged QTc interval, the mechanism of the DDI, clinical effects, values for normal QT intervals, and the drugs that generate the alert.

The website http://www.torsades.org of the University of Arizona distinguishes between drugs that are known for causing TdP (class 1), drugs with probable risk of causing TdP (class 2) and drugs that are unlikely to cause TdP (class 4).

METHODS

Setting

This study was conducted at the 1,237–bed Erasmus University Medical Center (Rotterdam, the Netherlands). All non-intensive care unit wards use the CPOE Medicatie/EVS® (Leiden, the Netherlands), which generates drug safety alerts for DDIs, overdose, and duplicate orders that are presented intrusively (Figure 1). Overridden drug safety alerts are routinely logged for pharmacy review.

Study population

All patients with overridden DDI alerts on QTc prolongation in Medicatie/EVS® version 2.20 between 1 February 2006 and 31 July 2006 in the Center Location of Erasmus MC were selected. Patients with ventricular pacemakers or treated on an outpatient basis were excluded, as were patients treated with the low-risk combination of tacrolimus with prophylactic, low dose cotrimoxazole (class 2 and 4 on http://www.torsades.org). Patients on long-term use of QTc-prolonging drugs with unknown start date or no longer using the combination of QTc-prolonging

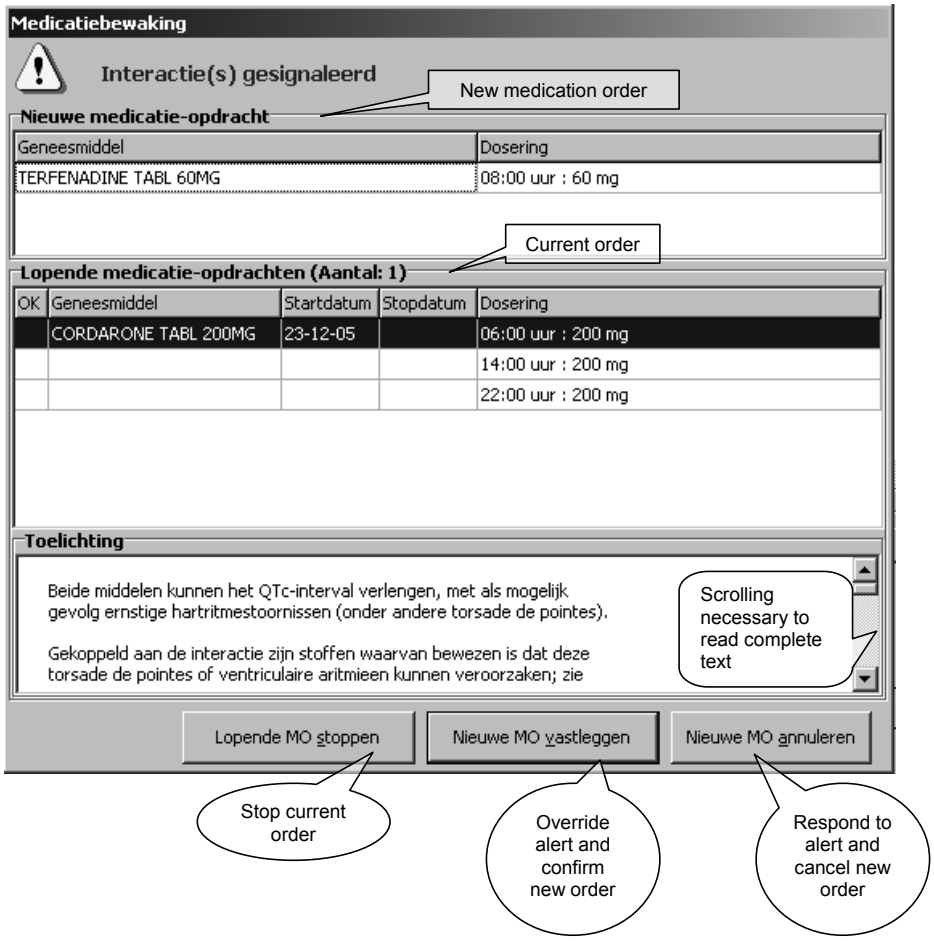

Figure 1 Example of a drug-drug interaction alert on QT prolongation
DDI alert presented to a physician ordering terfenadine (new order), when Cordarone (amiodarone; current order) is already on the patient's medication list.
The complete text can only be read if it is scrolled down. The translated text seen at a glance is:
Both drugs may prolong the QTc-interval and may possibly result in serious arrhythmias (Torsades de Pointes among others).
Drugs known for their potential to cause ventricular arrhythmias are linked to this drug-drug interaction; see

drugs were also excluded. For each patient in the cohort a sex- and age-matched control with two ECG recordings during use of one QTc-prolonging drug was selected in the same time frame to evaluate within-patient variability.

Data analysis

For each patient included, the interacting drugs, risk factors for TdP and digital ECG recordings (12-lead resting ECGs recorded with a Mortara electrocardiograph) were collected. Risk factors

for TdP were defined as: female gender, age > 65 years, presence of cardiovascular disease (myocardial infarction, heart failure, atrial fibrillation, hypertension, cerebrovascular accident, peripheral atherosclerotic vasculopathy), diabetes mellitus (use of glucose-lowering drugs) or renal failure (glomerular filtration rate < 50 ml/min) and potassium level < 3.5 mmol/l. Drugs were categorized using the classification of http://www.torsades.org. The QTc intervals were defined as prolonged if >470 ms for women and >450 ms for men. Increased risk of TdP was defined as QTc interval >500 ms or an increase of the QTc interval >60 ms upon addition of at least one QTc-prolonging drug. Statistical comparisons were performed with the Students' *t*-test (for independent samples) and Chi-square test in SPSS version 10.1 (SPSS Inc., Chicago, IL, USA).

Results

In the 6-month study period, DDI alerts on QTc prolongation were overridden in 368 patients; 200 patients were excluded for different reasons (Table 1).

Table 1 Patient selection

Patient category		Number
Patients with drug safety alerts on QT prolongation from 1 February to 31 July 2006		368
Patients excluded		200
Treated on an outpatient basis	35	
Using tacrolimus and low-dose cotrimoxazole	124	
Combination already discontinued	22	
Long-term use of combination (start date unknown)	7	
Ventricular pacemaker	4	
Other reasons	8	
Patients included		168

The inclusion criteria were met in 168 patients, and Table 2 shows the patient characteristics. For these 168 patients, 483 alerts were overridden with 70 different drug combinations. The majority of overridden alerts (91%) were due to at least one drug with a high risk of causing TdP (class 1). In 93% of the patients, besides the medication, there was at least one additional risk factor for TdP.

In 56 patients (33%) an ECG was made within 1 month after overriding the DDI alert and in 42 patients (25%) within 1 week of the prescription.

Differences between patients with and without an ECG being recorded are presented in Table 3. ECGs were more often recorded in patients suffering from cardiovascular disease and in patients with a higher average number of risk factors and overridden alerts. On cardiology wards, in 45% of the patients with overridden DDIs an ECG was recorded, whereas this occurred less often (31%) on other wards. However, this difference was not statistically significant.

In 49 patients (29%) an ECG before and after start of the drug that generated the QTc alert was available, allowing the change in QTc interval to be calculated. In 51% of these cases,

Table 2 Patient characteristics cohort

	Cohort (n=168)
Female gender	73 (44%)
Age > 65 years	87 (52%)
Cardiovascular disease	118 (70%)
Diabetes mellitus	43 (26%)
Renal failure (GFR < 50 ml/min)#	43 (30%)
Potassium level < 3.5 mmol/l$	10 (6.9%)
Average number of risk factors	2.2 ± 1.2 CI -0.2, 4.6
Average number of QTc-prolonging drugs	2.2 ± 0.4 CI 1.4, 2.9
2 QTc-prolonging drugs	139 (83%)
3 QTc-prolonging drugs	29 (17%)
No ECG	24 (14%)
ECG only before DDI	88 (52%)
ECG only after DDI	7 (4.2%)
ECG before and after DDI	49 (29%)
ECG after DDI within 1 week∇	42 (75%)
Pharmacists' advise to make an ECG∇	8 (14%)

Calculated on all patients in whom an estimated glomerular filtration rate was available (141);
$ Calculated on all patients with a measured potassium level (145); ∇ Calculated on all patients with an ECG after DDI overriding (56); CI 95% confidence interval; GFR glomerular filtration rate; DDI drug-drug interaction

Table 3 Patient characteristics for subjects with and without ECG recording after DDI overriding

	Post ECG (n=56)	No Post ECG (n=112)	P-value
Female gender	24 (43%)	49 (44%)	NS
Age > 65 years	29 (52%)	58 (52%)	NS
Cardiovascular disease	51 (91%)	67 (60%)	<0.001
Diabetes mellitus	18 (32%)	25 (22 %)	NS
Renal failure (GFR< 50 ml/min)#	20 (38%)	23 (26%)	NS
Potassium level <3.5 mmol/l $	3 (5.7%)	7 (7.6%)	NS
Average number of risk factors	2.6 ± 1.1 CI 0.3, 4.8	2.0 ± 1.2 CI –0.3, 5.2	<0.01
Average number of alerts per patient	4.4 ± 3.8 CI –3.3-12.0	2.2 ± 2.2 CI –2.2-6.5	<0.001
Average number of alert days per patient	2.8 ± 2.4 CI –2.0, 7.7	1.7 ± 1.2 CI –0.6, 4.1	<0.001
Combination of at least 2 class 1 drugs	23 (41%)	35 (31%)	NS
Cardiology ward	13 (23%)	16 (14%)	NS

Calculated on all patients in whom an estimated GFR was available (n=52 en 89, respectively)
$ Calculated on all patients with known potassium level (n=53 and 92, respectively)
CI 95% confidence interval; GFR glomerular filtration rate; NS not statistically significant

QTc-interval prolongation was found, and in 31% this was to such extent that the patient was considered at risk for TdP. Fifty-one percent of the patients were already using one QT-prolonging drug at the time of their first ECG recording.

The 25 patients in whom a prolonged QTc interval was found on the ECG made following DDI overriding are presented in Table 4. The number of risk factors ranged from one to five, and the drugs generating the alert ranged from high risk (class 1) to low risk (class 4). The majority of these patients (88%) were using two QT-prolonging drugs. One patient, not presented in Table 4 because his QTc interval remained <450 ms, was also considered at risk for TdP because he showed an increase in QTc interval of 75 ms upon starting the combined treatment with domperidone and amitriptyline (class 1 and 4). Two patients in whom the ECG criteria did not fulfil the criteria for an increased risk of TdP did develop ventricular arrhythmias, possibly due to the contribution of other risk factors. One patient used cisapride, which has been withdrawn from the market in certain countries in view of known risk of TdP in combination with several drugs.

For all patients with cardiovascular morbidity the type of cardiovascular disease and the cardiovascular drugs used are shown in Table 5. The average number of cardiovascular diseases in these patients was 1.5 and they used on average of 2.2 different cardiovascular drug classes.

For each case a control patient using one QTc-prolonging drug was selected to evaluate within-patient variability in the QTc interval. Patient characteristics presented in Table 6 show that the groups were similar, except for the first QTc interval. QT prolongation and risk of TdP were significantly more pronounced in cases with additional QT-prolonging drug(s) compared with the controls that continued one QT-prolonging drug. In the control group, the proportion of patients with an increased risk of TdP, based on QTc interval, did not change (10% for both first and second ECG), whereas in patients in whom an additional QTc-prolonging drug was started this percentage increased from 4 to 31%.

DISCUSSION

It was expected that a physician overriding a QTc-prolongation alert in the CPOE would decide to record an ECG within a period of about 1 week. This ECG could then be used for the decision whether continuation of the initiated combination was justified. However, ECGs were recorded in only a small percentage of patients with overridden QTc alerts (25% within 1 week, 33% within 1 month). Patients for whom an ECG was recorded more often suffered from cardiovascular diseases, had a higher number of risk factors for QTc prolongation and had a higher number of QTc overrides and more different days with QTc overrides. From our study we cannot distinguish whether ECGs were made because of cardiovascular comorbidity or because of the QTc alert. The percentage of ECGs recorded due to the alert only may even be <33%.

Several factors may explain why in only so few cases was an ECG recorded. First, the upper part of the alert text, which is seen at a glance (see Figure 1), draws attention to a serious adverse

Table 4 Subjects with prolonged QTc interval (n=25)

Patients are categorized according to number of risk factors

Gender	Age Yrs	Cardiovascular disease	Diabetes mellitus	GFR (ml/min)	K^+ level (mmol/ml)	Nr of risk factors	Drug 1	Drug 2	Drug 3	QTc2 (ms)	ΔQTc (ms)	Risk TdP
Female	75	+	+	13	4.1	5	*Haloperidol (1)*	*Amiodarone (1)*	-	504	29	+
Female	70	+	+	58	3.8	4	*Haloperidol (1)*	*Amiodarone (1)*	*Cotrimoxazole (4)*	487	47	-$
Female	71	+	-	37	4.2	4	*Indapamide (2)*	*Promethazin (NC)*	-	470	64	+
Male	54	+	+	33	4.3	3	*Haloperidol (1)*	*Pentamidine (1)*	-	499	49	-
Male	68	+	-	49	4.1	3	Amiodarone (1)	*Haloperidol (1)*	-	487	100	+
Male	72	+	-	48	3.9	3	Amiodarone (1)	*Ketanserin (NC)*	-	537	83	+
Male	94	+	-	25	4	3	Amiodarone (1)	Haloperidol (1)	*Claritromycine (1)*	461	19	-
Female	62	+	-	7	4.2	3	Amiodarone (1)	*Tacrolimus (2)*	-	592	201	+
Female	53	+	-	49	4.1	3	*Haloperidol (1)*	*Tacrolimus (2)*	-	530	62	+
Male	72	+	-	22	3.7	3	Indapamide (2)	*Haloperidol (1)*	-	462	30	-
Male	73	+	+			3*	*Domperidone (1)*	*Cotrimoxazole (4)*	-	453	25	-
Male	72	+	-	48	3.9	3	Sotalol (1)	*Erythromycin (1)*	-	501	32	+
Male	51	+	+	33	4.4	3	*Tacrolimus (2)*	*Mianserin (NC)*	-	510	122	+
Male	67	+	-	65	4.4	2	Sotalol (1)	*Haloperidol (1)*	*Cisapride (1)*	467	25	-
Male	68	+	-	>90	4.4	2	*Chloorpromazine (1)*	*Cisapride (1)*		490	64	+
Male	61	+	-	26	4.1	2	*Haloperidol (1)*	*Sotalol (1)*	-	478	84	+
Male	64	+	+	77	4.7	2	Sotalol (1)	*Amiodarone (1)*	-	502	73	+
Male	63	+	+		3.8	2*	*Sotalol (1)*	*Amiodarone (1)*	-	483	-29	-$
Male	64	+	+			2*	*Chloorpromazine (1)*	*Ketanserin (NC)*	-	467	91	+
Male	64	+	-	59	4.0	1	*Haloperidol (1)*	*Amiodarone (1)*	-	560	141	+
Male	41	+	-	69	3.9	1	*Haloperidol (1)*	*Amiodarone (1)*	-	475	48	-
Male	64	+	-	79	3.3	1	Sotalol (1)	*Claritromycine (1)*	-	485	10	-
Male	56	+	-	80	4.8	1	*Sotalol (1)*	*Amiodarone (1)*	-	464	24	-
Male	45	+	-	>90	4.2	1	*Haloperidol (1)*	*Tacrolimus (2)*	-	492	84	+
Male	36	+	-	60	3.7	1	Tacrolimus (2)	*Haloperidol (1)*	-	461	16	-

+ = present; - = absent; GFR = glomerular filtration rate in ml/min ; ( ) = drug class according to http://www.torsades.org; NC = drug not classified on http://www.torsades.org; QTc2 = QTc-interval after QTc-alert overriding; ΔQTc = change in QTc interval ECG before and ECG after QT alert; * = number of risk factors might have been higher due to unknown values; $= patient with ventricular arrythmias; Italics = QT-prolonging drug(s) started at time of QT alert

Table 5 Cardiovascular diseases and drugs

	Cohort n=168	Post ECG n=56	No post ECG n=112	Prolonged QTc interval n=25
Patients with cardiovascular disease	116	51	67	25
DISEASES				
Myocardial Infarction	17 (15%)	9 (18%)	8 (12%)	7 (28%)
Heart failure	25 (22%)	15 (29%)	10 (15%)	10 (40%)
Atrial fibrillation	33 (28%)	16 (31%)	17 (25%)	8 (32%)
Hypertension	49 (42%)	22 (43%)	27 (40%)	7 (28%)
Cerebrovascular accident	9 (8%)	6 (12%)	3 (4%)	2 (8%)
Peripheral atherosclerotic vasculopathy	4 (3%)	2 (4%)	2 (3%)	2 (8%)
Angina pectoris	14 (12%)	4 (8%)	10 (15%)	3 (12%)
Other cardiovascular disease	12 (10%)	0 (0%)	12 (18%)	0 (0%)
DRUGS				
Diuretics	55 (47%)	19 (37%)	36 (54%)	11 (44%)
Calcium channel blockers	20 (17%)	12 (24%)	8 (12%)	5 (20%)
Beta-blockers	68 (59%)	28 (55%)	40 (60%)	12 (48%)
RAAS-inhibitors	64 (55%)	32 (63%)	32 (48%)	21 (84%)
Nitrates	21 (18%)	8 (16%)	13 (19%)	4 (16%)
Digoxin	13 (11%)	6 (12%)	7 (10%)	3 (12%)
Amiodarone	16 (14%)	8 (16%)	8 (12%)	5 (20%)

Table 6 Patient characteristics cases (with QTc-alert overrides) and controls (using one QTc-prolonging drug)

	Cases (n=49)	Controls (n=48)	P-value
Gender female	20 (41%)	20(42%)	NS
Cardiovascular disease	44 (90%)	45 (94%)	NS
Diabetes mellitus	17 (35%)	18 (37%)	NS
Renal failure (GFR < 50 ml/min)#	19 (42%)	13 (33%)	NS
Mean age (years)	65 ± 12 CI 42, 88	62 ± 15 CI 32, 92	NS
Potassium level (mmol/l)	4.14 ± 0.49 CI 2.90, 4.86	4.24 ± 0.57 CI 3.11, 5.38	NS
Average QTc-interval ECG1 (ms)	430 ± 32 CI 366, 493	451 ± 37 CI 377, 524	<0.005
Average QTc-interval ECG2 (ms)	461 ± 44 CI 372, 549	447 ± 33 CI 381, 512	NS
Δ QTc (ms)	+ 31 CI –72, 133	- 4 CI –80, 72	< 0.001
Prolonged QTc-interval ECG1	7 (14%)	19 (40%)	< 0.005
Prolonged QTc-interval ECG2	25 (51%)	15 (31%)	< 0.05
Increased risk TdP ECG1	2 (4%)	6 (10%)	NS
Increased risk TdP ECG 2	15 (31%)	5 (10%)	< 0.025

Calculated on all patients with an estimated GFR (n=45 and 39, respectively)
CI 95% confidence interval; GFR glomerular filtration rate; TdP Torsades de Pointes

event (serious arrhythmias), but the words 'may' and 'possibly' weaken its impact. Furthermore, a recommendation to record an ECG is lacking in the first sentences and can be read only if the alert text is scrolled down. If the user decides to record an ECG, the CPOE provides no possibility of ordering it electronically. Even on cardiology wards with more understanding of the seriousness of TdP and with more possibilities for recording an ECG, alerts on QTc-prolonging drug combinations resulted in ECGs in only 45% of patients. Possibly, physicians assumed that despite the alert, the absolute risk of a serious arrhythmia remained low, and therefore overriding the alert would probably not result in adverse events.

Besides these problems on information content, low incidence, and handling possibilities, a specificity problem plays a role. Specificity has several aspects: relevance, urgency and accuracy. An alert is specific if it is not of minor importance (relevance), requires action (urgency) and is presented at the patient level, making use of gender, age, and serum levels (accuracy) [12]. The alerts on QTc prolongation are relevant because serious arrhythmias may result from overriding and only drugs with clinical evidence for TdP have been included in alert generation, and are urgent because the action of making an ECG is required, but they lack accuracy. Alert generation is not being tailored to female gender, older age, low potassium serum levels and bad renal function, and does not take into account comorbidity (cardiovascular disease, diabetes mellitus) and drug dose. This is caused by the fact that the majority of Dutch CPOEs do not have a link either with laboratory data or with clinical information of the patient.

It is unclear why ECGs were more often recorded in patients with a higher number of overridden alerts. We did not check the number of ECGs recorded, but only whether an ECG had been recorded, so it remains unknown whether a certain percentage of alerts did result in ECGs, or that a kind of alert threshold had to be exceeded before ECG recording took place. Furthermore, different physicians involved might have had different actions.

Error management

Drug safety alerts are incorporated in CPOE systems with the aim to make potential errors visible and thus prevent patient harm [13,14]. High sensitivity is strived for to limit the incidence of potentially dangerous prescribing errors. High specificity is necessary to prevent data overload.

To improve specificity substantially, all risk factors for developing TdP should be taken into account for alert generation. However, it is not clear to what extent the different risk factors add to the overall risk. These partial contributions should first be elucidated before accurate alert generation can take place. In case of combinations of QTc-prolonging drugs, ECGs just before and after combining such drugs should be recorded, and risk factors collected. Because of the urgency of the required action (preferably before starting the new drug), an unambiguous recommendation to record an ECG before and after starting a combination should be given in the first sentence of the alert text. If postponement of starting the drug combination is not desirable, a single ECG after combination can also give useful information. The hospital pharmacist can play a role in checking whether ECGs are recorded. If partial contributions of

risk factors for QTc prolongation are known, clinical rules incorporating this knowledge can be developed to improve specificity.

The advice to keep showing low specificity alerts to physicians seems contrary to the conclusion that high specificity is necessary to prevent data overload. Direction to someone else in the workflow, which is a useful alternative for low specificity alerts, is not feasible in case of QTc alerts because the action of ECG recording is urgent (should take place before starting the drug) and is necessary to quantify the risk of developing TdP. Without ECGs, someone else in the workflow cannot handle the alert either.

The fact that amiodarone is frequently involved in subjects with prolonged QTc interval or risk of TdP would suggest that special caution should be taken in patients using this drug. However, amiodarone has been shown to cause TdP rarely despite QTc-interval prolongation, which can probably be explained by its action on both sodium and calcium channels, preventing after-depolarizations [15].

Strengths and Weaknesses

This study has revealed the problem of a low percentage of ECGs recorded after QTc-alert overriding and has shown several causes for this overriding. Furthermore, it has shown an increase in the average QTc interval and in the percentage patients at risk for developing TdP in cases. Within-patient variability in the QTc interval was shown to be of minor importance by comparing cases with controls.

This study had several limitations. It was performed retrospectively during 6 months, in one hospital, with a relatively small number of patients with ECGs recorded before and after overriding QTc alerts. Unfortunately, alerts resulting in prescription cancellation cannot be logged by the system, so only overridden alerts could be studied. Motives for ECG recordings remained unknown and might be induced by alerts as well as other patient conditions, such as cardiovascular comorbidity. Potassium or creatinine levels were sometimes unknown due to the retrospective nature of the study and therefore the number of risk factors might be higher than calculated. Several comparisons did not reach statistical significance due to small patient numbers. The study was underpowered to predict which patients might develop TdP, and a prospective study should be performed to study the extent to which different risk factors add to the overall risk of TdP. We analysed QTc prolongation to assess the risk of TdP. Although this relationship is not clear-cut, this is the best way to study it, as TdP has a low incidence. Patients on the combination tacrolimus and cotrimoxazole were excluded from this study because of a perceived low risk of TdP, as these drugs are categorized in class 2 and 4 and the protocolized cotrimoxazole dose of 480mg daily to prevent *Pneumocystis carinii* infection is low. As several combinations with class 2 and class 4 drugs did result in considerable QTc prolongation with increased risk of TdP, it can be questioned whether this combination is really low risk.

The first ECGs of the control group and the cases were not comparable with respect to the QTc interval. This can be explained by the fact that the percentage of patients using one

QT-prolonging drug was 51% for cases and 100% for controls. This did not pose a problem, however, as the change in QTc interval was significantly more pronounced in cases than in controls.

CONCLUSIONS

Our study has shown that in only 33% of patients in whom a combination of two or more QTc-prolonging drugs had been initiated was an ECG recorded, despite the QTc alert shown to the prescribing physician. In those patients for whom an ECG was recorded, it remained unclear whether ECG recording was the result of the QTc alert or of other considerations. Patients with ECG recordings appeared to have more risk factors, more alert overrides and more days on which alerts were overridden.

For those subjects with ECGs before and after overriding the QTc alert, 51% had QTc-interval prolongation and 31% was considered at increased risk for TdP. This was due to many different drug combinations with drugs known for their potential to result in TdP as well as drugs unlikely to cause TdP or not classified as such.

QTc prolongation was statistically significantly more pronounced in the cases (due to addition of at least one QTc-prolonging drug) than in the control group that continued one QTc-prolonging drug. The low proportion of patients in whom an ECG was made following the alert, and the high prevalence of clinically important QTc prolongation in patients in whom ECGs were made, prompt us to recommend being more vigilant in such cases. Prescribing physicians should receive more information on the necessity of checking QTc intervals after initiating combinations of QTc-prolonging drugs. Pharmacists could send out reminders to those who do not comply.

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Chapter 3.5

Unintended consequences of reducing QT-alert overload in a computerized physician order entry system

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ABSTRACT

Purpose: After complaints of too many low-specificity drug-drug interaction (DDI) alerts on QT prolongation, the rules for QT alerting in the Dutch national drug database were restricted in 2007 to obviously QT-prolonging drugs. The aim of this virtual study was to investigate whether this adjustment would improve the identification of patients at risk of developing Torsades de Pointes (TdP) due to QT-prolonging drug combinations in a computerized physician order entry system (CPOE) and whether these new rules should be implemented.

Methods: During a half-year study period, inpatients with overridden DDI alerts regarding QT prolongation and with an electrocardiogram recorded before and within 1 month of the alert override were included if they did not have a ventricular pacemaker and did not use the low-risk combination cotrimoxazole and tacrolimus. QT-interval prolongation and the risk of developing TdP were calculated for all patients and related to the number of patients for whom a QT alert would be generated in the new situation with the restricted database.

Results: Forty-nine patients (13%) met the inclusion criteria. In this study population, knowledge base-adjustment would reduce the number of alerts by 53%. However, the positive predictive value of QT alerts would not change (31% before and 30% after) and only 47% of the patients at risk of developing TdP would be identified in CPOEs using the adjusted knowledge base.

Conclusion: The new rules for QT alerting would result in a poorer identification of patients at risk of developing TdP than the old rules. This is caused by the many non-drug-related risk factors for QT prolongation not being incorporated in CPOE alert generation. The partial contribution of all risk factors should be studied and used to create clinical rules for QT alerting with an acceptable positive predictive value.

INTRODUCTION

Many computerized physician order entry systems (CPOEs) generate drug safety alerts to remind physicians of potentially unsafe situations. Drug safety alerts are frequently overridden, for example because the alert is not patient-tailored, or because the disadvantages of the situation do not outweigh the advantages. A high number of low-specificity alerts may cause physicians to override important alerts along with unimportant ones, thereby decreasing safety [1].

In the Netherlands, all hospital CPOEs make use of the national drug database, which is updated monthly. This G-standard contains safety information for all drugs licensed in the Netherlands [2]. The G-standard introduced drug-drug interaction (DDI) alerting on QT prolongation in March 2005. QT prolongation may predispose patients to developing Torsades de Pointes (TdP) and to sudden cardiac death. After many complaints about low-specificity alerts in the CPOEs, several drugs were excluded from QT-alert generation in May 2007 [3,4] without any outcome measurements.

The aim of this study was to compare the rules for QT alerting to see whether the 2007 rules would identify patients at risk of developing TdP better than the 2005 rules.
The following questions were to be answered:

1. In what percentage of patients at risk of developing TdP due to a combination of two QT-prolonging drugs is a QT-prolongation DDI alert generated (sensitivity)?
2. In what percentage of generated QT-prolongation DDI alerts is the patient really at risk of developing clinically significant QT prolongation (positive predictive value of the QT alert)?

BACKGROUND

Many cardiac and noncardiac drugs can prolong the QT interval on the electrocardiogram (ECG), thereby increasing the risk of serious ventricular arrhythmias (e.g., TdP) and sudden cardiac death. TdP has a low incidence, and the prolongation of the absolute QTc interval beyond 500 ms and/or an increase of more than 60 ms are regarded as leading to an increased risk of TdP [5-7].

Many risk factors may increase the risk of developing TdP such as gender, age, cardiovascular disease, and electrolyte disturbances; elderly females are especially at risk. Many drugs increase this risk to different extents, and higher doses and renal failure may add an additional risk [5,7].

The Dutch national drug database, the G-standard, has included DDI alerts on QT prolongation since March 2005 [8]. At first, drugs from lists D and E from De Ponti [9,10] generated this alert, as well as all class Ia and III antiarrhythmics [4]. List D contained all drugs clinically associated with TdP, and list E included drugs with clinical evidence for TdP plus an official warning of causing TdP [8-10]. In 2006 a discussion took place about the relevance and urgency of this DDI. Some hospital pharmacists concluded after studying the literature that many combinations

were of minor importance with no need for action [8,11], although hospital pharmacists responsible for the DDI alerts in the G-standard disagreed [12-14].

Since May 2007 Dutch QT alerting has been based on the system of the Arizona Center for Education and Research on Therapeutics [15]. This system earlier consisted of four drug classes with a different risk of causing TdP: class 1 drugs were known to cause TdP, class 2 drugs had a probable risk and class 4 were unlikely to cause TdP. Class 3 drugs were contraindicated in patients with long (congenital) QT syndrome [3]. At present three categories exist: drugs with a risk of causing TdP (formerly class 1), drugs with a possible risk (formerly class 2) and drugs with a conditional risk (including the former class 4 drugs) [15].

In May 2007, the G-standard limited DDI alerting for QT prolongation to combinations of class 1 drugs and terfenadine and adjusted the information content of the alert text (See Figures 1 and 2). Furthermore it introduced contraindication alerting for patients with a prolonged QT interval taking single drugs from classes 1 and 2, sympathicomimetic drugs or terfenadine. The new rules for DDIs resulted in a reduction in the number of drugs generating the QT alert (from 30 to 20) and were based on expert opinions formulated after studying and discussing the available literature. Outcome measurements were not performed [3].

Both drugs may prolong the QTc interval.

Recommendation:
Use of several QTc-prolonging drugs may result in a higher risk of serious arrhythmias. The risk should be considered per patient.

Patient WITHOUT risk factors: the risk of ventricular arrythmias is low.
Patient WITH risk factors: use of the combination is discouraged, or make an ECG before starting the medication.

Risk factors for prolonged QTc interval:

Figure 1 First part of the old alert text

METHODS

Setting

The 1,237–bed Erasmus University Medical Center, Rotterdam, the Netherlands, uses the CPOE Medicatie/EVS® (Leiden, the Netherlands) [16] on all wards except ICUs. This CPOE system for prescribing medication generates intrusive drug safety alerts for DDIs, overdoses and therapeutic duplications based on information held in the G-standard database. Overridden drug safety alerts are routinely logged for pharmacy review.

Both drugs may prolong the QTc interval and may possibly result in serious arrhythmias; symptoms are sudden dizziness or syncope. In the last extremity resulting in sudden cardiac arrest.

Recommendation:
A concrete recommendation cannot be given because cut off points for the decision are difficult to define. Several risk factors can be deduced from comedication, for example diuretics (hypokalemia), or digoxin or a renin-angiotensin-aldosterone-system inhibitor (heart failure). The risk should be weighted per patient. Essentially, the combination should be avoided (for example by replacing domperidone by metoclopramide). If this is impossible, an ECG should be recorded.

QTc prolonging drugs are contraindicated in case of long QT syndrome or acquired prolonged QT interval. Alerting for this can be arranged by the contraindication prolonged QT interval.

Risk factors for prolonged QT interval:

Figure 2 First part of the new alert text

Study population

All overridden QT-prolongation DDI alerts generated in Medicatie/EVS® version 2.20 between 1 February 2006 and 31 July 2006 in the Erasmus MC-Center location (a general hospital) were used for patient selection. Outpatients, patients with ventricular pacemakers, transplanted patients treated with the low-risk combination of tacrolimus with cotrimoxazole (class 2 and 4), patients who were long-term users of QT-prolonging drugs with unknown start dates or who were no longer using the combination were excluded. The secondary inclusion criterion was patients with ECGs available from before and within 1 month of the QT-alert override.

Measures

For each patient included, the interacting drugs, risk factors for TdP, and digital ECG recordings (12-lead resting ECGs recorded with a Mortara electrocardiograph) were collected. Risk factors for TdP were defined as female gender, age > 65 years, presence of cardiovascular disease (myocardial infarction, heart failure, atrial fibrillation, hypertension, cerebrovascular accident, peripheral vasculopathy), diabetes mellitus (use of glucose-lowering drugs), renal failure (glomerular filtration rate < 50 ml/min), and potassium level < 3.5 mmol/l. Increased risk of TdP was defined as QTc interval > 500 ms or an increase of the QTc interval > 60 ms [6]. Sensitivity was calculated as true positives/(true positives + false negatives). Positive predictive value was calculated as true positives/(true positives + false positives).

RESULTS

In the 6-month study period, DDI alerts on QT prolongation were overridden for 368 patients. 319 of these patients were excluded for different reasons (Table 1). The most frequent reasons for exclusion were the use of tacrolimus and low-dose cotrimoxazole in transplant recipients (n=124, 34%), the unavailability of ECG recordings before and after initiation of the drug combination (n=119, 32%), and the patient being treated on an outpatient basis (n=35, 9.5%).

Table 1 Patient selection

Patient category		Number
Patients with overridden drug safety alerts on QT prolongation from 1 February - 31 July 2006		368
Patients excluded		319
Treated on an outpatient basis	35	
Using tacrolimus and low-dose cotrimoxazole	124	
Combination not used any more	22	
Long-term use of combination (start date unknown)	7	
Ventricular pacemaker	4	
Other reasons	8	
< 2 ECGs	119	
Patients included		49

Forty-nine patients met the inclusion criteria; Table 2 presents the patient characteristics. The mean number of non-drug-related risk factors was 2.7 (SD 1.1). All patients had at least one non-drug-related risk factor for developing TdP.

Table 2 Characteristics of patients meeting the inclusion criteria (n=49)

Characteristic	Number (%)
Female gender	20 (41%)
Cardiovascular disease	44 (90%)
Diabetes mellitus	17 (35%)
Renal failure[#]	19 (42%)
Age > 65 years	29 (59%)
Potassium level < 3.5 mmol/l[$]	3 (6.7%)

Calculation based on all patients for whom an estimated glomerular filtration rate was available (n=45)
$ Calculation based on all patients with a measured potassium level (n=45)

Fifteen patients (31%) were considered at risk for developing TdP; Table 3 shows their patient characteristics. All at-risk patients used two QT-prolonging drugs, ranging from high risk (class 1) to low risk (4). The number of non-drug-related risk factors per patient ranged from 1 to 5.

In the new database since May 2007, many frequently encountered combinations of QT-prolonging drugs no longer generate a DDI alert in the CPOE. The last column of Table 3 shows whether combinations would result in a QT alert in the new situation. For 8 of the 15 patients with increased risk of TdP in our study (53%) no alert would be generated with the new rules

Table 3 Subjects at risk of Torsades de Pointes (n=15)
Patients are categorized according to number of non-drug-related risk factors

Gender	Age	Cardio-vascular disease	Diabetes mellitus	GFR (ml/min)	K^+ level (mmol/l)	Risk factors	Drug 1	Drug 2	QTc2 (ms)	ΔQTc (ms)	New alert
Female	75	+	+	13	4.1	5	*Haloperidol (1)*	*Amiodarone (1)*	504	29	+
Female	71	+	-	37	4.2	4	*Indapamide (2)*	*Promethazine (NC)*	470	64	-
Male	68	+	-	49	4.1	3	Amiodarone (1)	*Haloperidol (1)*	487	100	+
Male	72	+	-	48	3.9	3	Amiodarone (1)	*Ketanserin (NC)*	537	83	-
Female	62	+	-	7	4.2	3	Amiodarone (1)	*Tacrolimus (2)*	592	201	-
Female	53	+	-	49	4.1	3	*Haloperidol (1)*	*Tacrolimus (2)*	530	62	-
Male	72	+	-	48	3.9	3	Sotalol (1)	*Erythromycin (1)*	501	32	+
Male	51	+	+	33	4.4	3	*Tacrolimus (2)*	*Mianserin (NC)*	510	122	-
Female	81	+	-	80	3.6	3	*Domperidone (1)*	*Amitriptyline (4)*	438	75	-
Male	68	+	-	>90	4.4	2	*Chlorpromazine (1)*	*Cisapride (1)*	490	64	+
Male	61	+	-	26	4.1	2	*Haloperidol (1)*	*Sotalol (1)*	478	84	+
Male	64	+	+	77	4.7	2	Sotalol (1)	*Amiodarone (1)*	502	73	+
Male	64	+	+			2*	*Chlorpromazine (1)*	*Ketanserin (NC)*	467	91	-
Male	64	+	-	59	4.0	1	*Haloperidol (1)*	*Amiodarone (1)*	560	141	+
Male	45	+	-	>90	4.2	1	*Haloperidol (1)*	*Tacrolimus (2)*	492	84	-

+ Present, - absent, *GFR* glomerular filtration rate in ml/min, *QTc2* QTc interval after QTc-alert override, Δ*QTc* change in QTc interval between ECGs before and after QTc alert
Numbers in parentheses indicate drug class according to www.torsades.org,
NC = not classified on www.torsades.org
Italics = QTc-prolonging drug(s) started at time of QTc alert
* = number of risk factors might have been higher due to unknown values

because the drugs are 'not classified' or do belong to classes 2 or 4. Assuming the CPOE with the old 'inclusive' drug database identified all patients at risk of developing TdP, the modified database would result in a sensitivity of 47%. Table 4 shows whether an alert would be generated for patients at risk of developing TdP in the new situation. Twenty-three rather than 49 alerts would be generated (47%). The positive predictive value in the study population was 31% (15/49) in the old situation and would be about the same (30%,7/23) if the CPOE would make use of the modified database.

Table 4 Numbers of patients at risk of developing Torsades de Pointes for whom a QT-prolongation DDI alert is generated in the new situation (database restricted to obviously QT-prolonging drugs)

	Alert generated (n)	No alert generated (n)
Patients at risk of TdP	7 (true positives)	8 (false negatives)
Patients not at risk of TdP	16 (false positives)	18 (true negatives)

DISCUSSION

The decreased number of drugs generating QT alerts successfully lowers the alert numbers in our study population from 49 to 23. However, it does not address the specificity problem

adequately, as the positive predictive value does not change. Furthermore, the QT-rule modification introduces a sensitivity problem as the new system would miss 53% of the patients at increased risk of developing TdP. Reduction of the QT-alert overload by excluding several drugs from QT-alert generation clearly has unintended and undesirable consequences.

One question is whether these results can be extrapolated to the entire inpatient population. Only inpatients with an ECG before and within 1 month of QT-alert overriding were included. Thirty-two percent of the patients with QT-alert overrides were excluded because ECGs were not available to calculate the QT interval, and these could have been low-risk patients. However, the excluded patients had a considerable average number of non-drug-related risk factors: 2.0 (SD 1.2). The patients included had a higher average number of 2.7 (SD 1.1), which could have led to an overestimation of the proportion of patients considered to be at risk.

None of the patients in our study had zero non-drug-related risk factors, and it is likely that these risk factors for developing TdP (e.g., cardiovascular disease) led to an overestimation of the positive predictive value. Inclusion of the entire inpatient population would have resulted in an even lower positive predictive value.

Furthermore, patients using the combination tacrolimus and cotrimoxazole were excluded, because this very frequently used combination in transplanted patients in the Erasmus MC was perceived not to result in TdP. It can be questioned, however, whether this assumption is correct [17]. If the combination really is a low-risk combination not resulting in TdP, inclusion of these patients would have resulted in a higher positive predictive value.

How can these unintended consequences be understood? QT prolongation is dependent on age, gender, comorbidity, serum potassium level, renal function, drug class, and drug dose. Although age and gender of the patients are known in our CPOE, these items were not used in QT-alert generation and suppression. QT-alert generation in Medicatie/EVS® was and is only dependent on drug class and is not tailored to at-risk patients, so accuracy remains low. Furthermore, the drugs now excluded from QT-alert generation are known to have a probable or unlikely risk of causing TdP when used as single drugs, but the effects of combinations of these drugs in patients with non-drug-related risk factors are unknown.

Error management

How should the problem of these low-specificity alerts be managed? Ideally, QT alerts would only be generated for patients really at risk of developing TdP and they would be suppressed if the risk is low [18]. However, to calculate the overall risk of developing TdP, the contributions of all risk factors, including drug class and dose, should be known. This information is not known, and therefore effective filtering of QT alerts for at-risk patients is not feasible. Only by prospectively collecting ECGs before and after the initiation of combinations of two or more QT-prolonging drugs will we be able to determine the true risk of developing clinically relevant QT prolongation. It is only with this knowledge that QT alerts with both high sensitivity and specificity (positive predictive value) can be developed. An acceptable positive predictive value is open to debate.

Bates proposed an override rate of less than 40% for strongly action-oriented suggestions [19], but this seems to have been chosen arbitrarily. If however this recommendation were to be followed, the current positive predictive value of DDI alerts on QT prolongation should be doubled.

We recommend that ECGs should be performed before and within 1 week of the QT override. If postponement of this drug therapy were undesirable, a single ECG after the QT override would also give useful information. This recommendation to record an ECG should be presented as a clear message during the order entry process. Both old and new alert texts are rather long and complicated (Figures 1 and 2), and it is easy to modify the messages. It would be very helpful if ECGs could be ordered from the CPOE, but this type of integration is largely absent in Dutch hospital CPOEs.

The drug lists on www.torsades.org are regularly updated in contrast to the De Ponti list [3,15]. The lists at first only included drugs that were on the market in the United States. Fortunately, drugs that are not (and no longer) available in the US (terfenadine, domperidone) are included now. For the Dutch situation it should be kept in mind however that ketanserin, mianserin and promethazine are absent on www.torsades.org [3,15].

Strengths and Weaknesses

This study had several limitations. It focused on the risk of TdP by analyzing QT prolongation. Although this relationship is not clear cut, this is the best way to study the risk of developing TdP, as TdP has a low incidence [5-7]. QT intervals show high diurnal variability, may be subject to reading errors, and are dependent on drug serum level [5-7,20,21]. The ECGs in this study were not recorded under standardized conditions, and this might have resulted in less accurate QT intervals. This study did not aim to identify risk patients with a high certainty, but mainly focused on the difference between old and new rules for QT-prolongation alerts in a CPOE. It elucidated a problem requiring a prospective study including ECGs recorded under standardized conditions and taking into account drug serum levels.

Due to QT-interval variability, it can be questioned whether it is correct to use absolute QT intervals >500ms or QT prolongation >60ms as the best identification of patients at risk of TdP [20,21]. We used both measures according to the guidelines of the European Medicines Agency and only used the categories with most marked increases to reduce the effect of QT variability [6].

DDIs may have been generated by adding one QT-prolonging drug to an existing therapy containing another QT-prolonging drug, but may also have been the result of two newly-prescribed QT-prolonging drugs. Twenty-five patients (51% of the patients included) already used one QT-prolonging drug, resulting in a smaller increase in QT interval and a higher probability of exceeding the limit of 500ms. This was another reason to include both QT-interval measures to identify patients at risk of TdP.

A weakness of this study is that the study population may differ from the whole patient population. Selection may have been biased, because patients taking the combination tacrolimus-cotrimoxazole (34%) and patients without 2 ECGs (32%) and with a lower number

of non-drug-related risk factors were excluded. It is unlikely however that inclusion of the tacrolimus-cotrimoxazole combination would change our conclusions that the new rules are worse. This combination does not result in alert generation with the adjusted rules. If it were a low-risk combination, inclusion would increase the positive predictive value but the sensitivity would remain low. If it were a high-risk combination inclusion would result in a decreased positive predictive value and sensitivity. Both effects are unintended.

The modifications of the G-standard excluded 11 drugs generating QT alerts and added 1 drug: arsenic trioxide. This could have had an effect on the sensitivity and positive predictive value, but this drug was not prescribed in our CPOE in the study period.

A drawback of the CPOE used in this study is that only overridden alerts are logged for pharmacy review. Alerts resulting in order cancellation are not available, and override reasons are not required. Disguised observation in the Erasmus MC revealed an override rate of > 90% for DDIs, including QT-prolongation alerts [22].

Notwithstanding these limitations this study clearly showed the unintended effects of a proposed measure to reduce alert overload on patient safety, making use of patient data from normal clinical practice.

CONCLUSION

Reducing QT-alert overload by excluding drugs without proven risk of causing TdP from alert generation would result in a considerable reduction in alert numbers, would not change the positive predictive value, and would introduce a sensitivity problem. The high number of non-drug-related risk factors that are not included in QT-alert generation could explain these unintended consequences. Further outcome measurements should be performed to elucidate the contribution of the non-drug-related risk factors to the overall risk. Ideally, clinical rules incorporating all risk factors could then be developed to generate QT alerts with an acceptable positive predictive value.

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Chapter 4

General discussion

INTRODUCTION

Pharmacotherapy is one of the most frequently used forms of medical treatment in modern healthcare. However, medication errors are a frequent cause of errors with considerable healthcare costs. Prescribing drugs electronically is considered an important measure to reduce medication errors. A system enabling clinicians to prescribe drugs electronically is called a computerized physician order entry (CPOE) system. CPOE systems often include integrated decision support components that attempt to improve clinicians' decisions through advice, alerts and reminders. Studies documenting positive effects of decision support on patient outcomes have prompted calls for additional patient-specific advice. On the other hand, if the burden of alerts is too high, alert fatigue may cause physicians to override both important and unimportant alerts, in a manner that compromises the desired safety effect of integrating decision support into CPOE.

This thesis focused on drug safety alerting in CPOE. The overall aim of the studies was twofold: to gain an insight into drug safety alert generation and overriding, and to study the effects of attempts to decrease the burden of excessive numbers of drug safety alerts. In this chapter we discuss why we used several different quantitative and qualitative methods to unravel and counteract alert fatigue. Furthermore, we discuss whether the model for the interpretation of erroneous drug safety handling proposed in chapter 2.1 is useful and/or should be adjusted. After that, we discuss whether we succeeded in unraveling and counteracting alert fatigue. This chapter ends with recommendations for improvement and future research.

METHODOLOGY

The process of alert generation and handling can be summarized as shown in Figure 1. The knowledge base and the CPOE determine alert generation; physicians have to handle these alerts, and this handling has effects on the patient for whom orders are entered. Furthermore, pharmacists responsible for the quality of drug safety alerting and nurses administering drugs are involved.

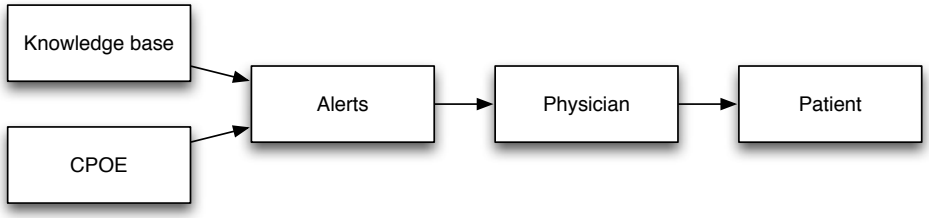

Figure 1 Process of alert generation and handling

We studied behavior and explanations for it, opinions, computer performance and patient effects. To grasp all these (technical and human) aspects we used observations, interviews, questionnaires, quantitative analysis of pharmacy log files, chart review, and a computer test as research techniques. Furthermore we used retrospective and prospective, quantitative and qualitative study designs, field and laboratory studies.

In medical informatics, the nature of the research questions often requires a combination of qualitative and quantitative methods. Only with such 'mixed methods' can all different aspects and effects of information systems be captured [1]. Qualitative studies, like observations and interviews, are useful to understand a phenomenon and to identify areas requiring investigation: What is happening? Why and how? Qualitative research is often used as a starting point for further quantitative research that evaluates the size and extent of the phenomenon, or statistically proves that it is indeed present. On the other hand, qualitative methods can also help to interpret quantitative results. Quantitative methods cannot answer the question why a phenomenon is present and how it should be explained. On the other hand qualitative methods are not suited for quantification of the phenomenon. By using results from one study as input for the other, weak points from one method might be counteracted and strong points capitalized upon.

A measure to reduce bias and enhance validity is triangulation: testing the same variables in different ways instead of using a single method. Triangulation can take three different forms: methodological triangulation (the use of several methods to collect the data and multiple measurements within the same method), data triangulation (data collected at different times and places from different people and groups) and theory triangulation (use of more than one theoretical approach to the analysis) [2]. In this thesis methodological triangulation was used in the majority of studies. Theory triangulation was lacking as we used one theoretical approach. We applied Reason's model of accident causation to drug safety alerting and presented the following model to interpret how an alerting system designed to prevent errors may provoke them (Figure 2). In the following subsections we discuss how we translated our research questions into study designs, and whether the same results would have been obtained and the same conclusions drawn without triangulation. Thereafter we discuss investigator bias.

The following research questions were addressed in this thesis:

1. How often and in what kind of situations are safety alerts overridden?
2. Why do physicians override them?
3. What kind of errors are made in alert handling?
4. What is the quality of drug safety alerting in Dutch CPOE systems?
5. Can the burden of excessive numbers of drug-drug interaction alerts be decreased safely by
    a. Turning off frequently overridden alerts?
    b. Adding levels of seriousness to the alert text?
    c. Directing alerts to other people in the workflow?
    d. Increasing specificity?

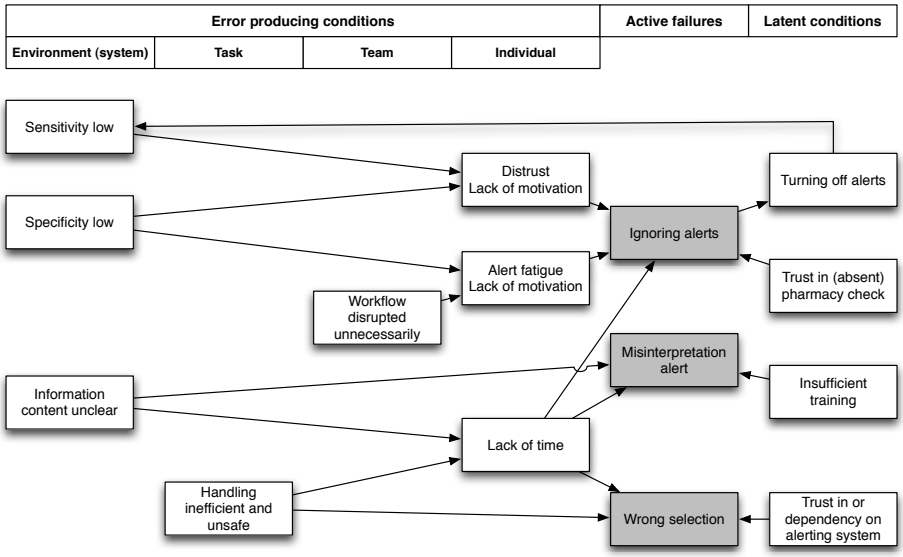

Figure 2 Reason's model of accident causation applied to drug safety alerts in CPOE

How often and in what kind of situations are safety alerts overridden?

To answer this question, we had to quantify the number and type of drug safety alerts generated and overridden. Alerts that are generated and subsequently annulled (by cancellation or adjustment of orders) are not logged in the CPOE used in the Erasmus University Medical Center (Medicatie/EVS®). Therefore, the best way to measure the number of alerts generated and to calculate the override rate, was observation in a field setting. Because observation is inefficient with respect to time, we performed it only for one (frequently prescribing) specialty.

The easily available pharmacy log files only contained overridden alerts. Retrospective analysis of these files could be performed efficiently and revealed information for the entire hospital over a longer study period.

The combination of observation and retrospective analysis of pharmacy log files described in chapter 2.2 gave a clear insight into quantitative aspects of alert generation and overriding that could not be obtained efficiently with one of the methods performed alone.

Why do physicians override drug safety alerts? What kind of errors are made in alert handling?

We used the model presented in Figure 2 for the simulation study described in chapter 2.3. To study whether active failures (ignoring and misinterpretation of alerts and wrong selection) were present, a disguised observation study with interviews directly afterwards was most appropiate.

We wanted to study error-producing and latent conditions as much as possible within a relatively small time frame. Therefore, we designed a laboratory study with different alert types (drug-drug interactions (DDIs), duplicate orders and overdoses) of varying familiarity. A

time-dependent DDI alert was included to study whether physicians perceived this alert as 'unnecessarily disrupting workflow'. A sequence-dependent alert that should not be overridden was included to study 'low specificity' as an error-producing condition. Unknown DDIs were used to study whether the 'information content' was clear. To study 'trust in, or dependency on, alerting system', overdoses of unfamiliar drugs were included.

To simulate physicians' normal work environment, we created a patient handover before, and a noisy atmosphere, time pressure, and distraction during, order entry. For validation, we asked afterwards whether the laboratory session had resembled the normal work environment.

If we had performed interviews only, unconscious and unintended actions could not have been studied. On the other hand, if we had observed only, reasons for (erroneous) handling and resemblance to the normal work environment would have remained unknown.

What is the quality of drug safety alerting in Dutch CPOE systems?

All Dutch hospital CPOEs use the same knowledge base, the G-standard. This Dutch drug database contains safety information for all drugs licensed in the Netherlands. We decided that good drug safety alerting requires highly specific alerts that are generated in all dangerous situations (high sensitivity). To find out whether the sensitivity and specificity of our CPOE system (Medicatie/EVS®) was high or low, we had to compare our CPOE system with those of other Dutch hospitals, as there was no gold standard for testing. Alert generation depends on functionality of the CPOE, content of the knowledge base, local knowledge base adjustments and local CPOE configurations. To enable us to study functionality differences, we minimized the effect of the latter three (same knowledge base, testing in offices of software vendors, two patient cases per test item that had to show similar results and three patient cases with similar results after local configuration). To ensure reliability, the test was checked for completeness and correctness with the latest version of the Dutch drug database at the Royal Dutch Association for the Advancement of Pharmacy (KNMP) office. We used the quantitative results of this computer test to interview hospital pharmacists about the relevance of missing functionality.

Without the interviews the interpretation of the impact of the test results would have been difficult, as the perceived relevance of lacking functionality appeared to depend on the organization. If we had only interviewed hospital pharmacists about the quality of drug safety alerting in their CPOE, we would only have compiled a snapshot of subjective opinions. Our new test can be used as a monitoring tool to select and improve future CPOE systems.

Can the burden of excessive numbers of drug-drug interaction alerts be decreased safely by turning off frequently overridden alerts?

Quantitative results from retrospective analysis of pharmacy log files were used to select the DDIs with the highest likelihood of causing alert fatigue. Turning off these alerts without investigation would certainly decrease the number of DDI alerts, but would possibly also result in patient harm due to decreased sensitivity and was therefore deemed inappropriate. As

reasons for frequent overriding and a good measure for the burden of excessive alerting were largely unknown, qualitative interviews were selected as the best study method to answer the abovementioned question. The interviews were performed one-to-one to prevent individual opinions changing under the influence of a group of respondents. We included both specialists and residents from different specialties to capture opinion differences between those groups.

The interviews described in chapter 3.1 revealed a variety in opinions and reasons for their decisions whether to turn off alerts. Furthermore, even within one hospital differences appeared to be present in routine monitoring. The results from the 576 assessments in the interviews were subsequently used quantitatively and revealed a positive correlation between the number of alerts overridden and the decision to turn off, which would have remained hidden by qualitative methods alone.

Can the burden of excessive numbers of drug-drug interaction alerts be decreased safely by adding levels of seriousness to the alert text?

In chapter 3.2 we used a before-after design using pharmacy log files to investigate the effect of addition of level of seriousness in the alert text and combined it with questionnaires given to physicians who had been exposed to the new alert texts. If we had only performed interviews we would not have been able to measure the unexpected increase in override rate. On the other hand, if we only had measured override numbers from the pharmacy log files we would have considered the measure to be useless. We performed a sensitivity analysis to compensate for the lack of logged annulled alerts.

One might ask why we did not perform a randomized clinical trial (RCT) to answer this question. RCTs in medicine generally compare large groups of patients using a drug or placebo. Patients are randomly assigned to one of the two groups and physicians and nurses are generally blinded for the therapy given. In a RCT to evaluate adding the level of seriousness, for example physicians would have to have been randomly assigned to different alert presentations (with or without level of seriousness presentation) but that appeared to be technologically impossible within our hospital. An alternative approach would have been to put both versions on a test computer and ask physicians to use it in a test environment. This would have created a laboratory session not resembling the normal work environment and blinding would not have been possible. Another possibility would have been to test the intervention in one hospital and to compare it with the old system in another hospital. However procedures and work routines may differ significantly between hospitals rendering groups of physicians non-comparable. We therefore decided to perform a prospective intervention study with a before-after design.

Can the burden of excessive numbers of drug-drug interaction alerts be decreased safely by directing alerts to other people in the workflow?

To answer this question we selected the category 'time-dependent DDIs'. These are DDIs that indicate that a time interval between administering different drugs is required. As nurses

generally administer drugs to patients, we hypothesized that they would be the key people to handle DDIs with respect to drug administration times. We used the percentages of drug administration errors as a safety measure. We performed two intervention studies with a before-after design with an interval of two years on 8 and 28 wards respectively. The second study enabled us to investigate whether nurses' corrections of prescribing errors were present throughout the hospital and could be formalized.

In chapter 3.3 we used the quantitative results of nurses preventing drug administration errors by correcting physicians' prescribing errors to propose a formalization of their handling. Although this was the most logical way to reduce errors, head nurses and medical coordinators did not agree upon changing responsibilities in this field. This outcome shows the organizational entanglement of the CPOE, and the necessity of change management that takes into account the social context.

Can the burden of excessive numbers of drug-drug interaction alerts be decreased safely by increasing specificity?

A nationally proposed adjustment in the G-standard to increase the specificity of alerts on QT prolongation was the starting point of the studies described in chapters 3.4 and 3.5. QT prolongation was used as a measure of safety but the QT interval can only be calculated if an electrocardiogram (ECG) is performed. Therefore, we investigated the percentage of patients with overridden QT alerts for whom an ECG was recorded. Furthermore, we investigated the relevance of the alerts by comparing QT prolongation of a patient group with overridden QT alerts with a control group with one QT-prolonging drug. The rule for QT alerting in the G-standard was changed after complaints about the poor signal-to-noise ratio of these alerts that were not backed by evidence. We doubted whether the G-standard adjustment could be performed safely and decided not to implement it without investigation. We therefore used the retrospective data from chapter 3.4 for a virtual study described in chapter 3.5. We exclusively used quantitative methods to measure numbers of ECGs and patients at risk of developing Torsades de Pointes.

Triangulation between studies

Besides triangulation within studies, results between studies can also be triangulated, as several alerts were used in the simulation study described in chapter 2.3 as well as in the study on turning off (chapter 3.1). In the latter study, respondents suggested suppressing the combination of insulin and selective beta-blockers (DDI 0302) for internal medicine. In the simulation study all physicians handled this DDI correctly, suggesting that this DDI could indeed be turned off safely. The same was true for the DDI regarding the combination of beta-blockers and NSAIDs (0272).

Internists also asked to turn off the most frequently overridden DDI 0019. This DDI is only relevant if ACE inhibitors are started in a patient already using diuretics, and is irrelevant in the

majority of cases (when diuretics are started in patients on ACE inhibitors). The first situation was present in the simulation study and was handled incorrectly by the majority of physicians. The high frequency of justified overriding of this low-specificity alert probably provoked this behavior. Chapter 2.4 showed that several CPOEs had functionality to use sequence indications from the Dutch drug database to prevent unnecessary alerts of this type. Developing this functionality for Medicatie/EVS® is therefore preferable to turning off the sequence-dependent alerts.

Physicians unanimously said that the DDI alert on QTc prolongation (5088) should not be suppressed because people do not check the QT interval on the ECG on a regular basis. This finding was confirmed in the simulation study, in which physicians often said ECG recording was not necessary. Chapter 3.4 furthermore showed that ECGs were performed infrequently when QT alerts were overridden.

The DDI for the combination of NSAIDs and SSRIs (3360) was said to be little known and was not a perceived candidate for turning off. This DDI was also generated in the simulation test but was often overlooked, probably because it was presented as a second alert in one alert pop-up. So the results of these studies cannot be compared.

Time-dependent DDIs were not included in the study on turning off alerts, because directing them to other people in the workflow was thought to be a better alternative than turning them off. The time-dependent DDI alert in the simulation test was handled incorrectly many times and one 'justification' for overriding was the fact that nurses would handle these alerts. Although nurses often adjusted administration times to obtain the required time interval, this procedure had not been formalized and the ward management was unwilling to implement it.

Investigator bias

Our research group consisted of:

- a hospital pharmacist who had been involved in introducing the CPOE and its integrated drug safety alerting,
- an internist/clinical pharmacologist using the CPOE as a prescribing physician, and with an interest in drug safety alerting,
- a medical informatics specialist involved in research on CPOE implementation, CPOE use, and the corresponding changes in work processes,
- a professor in social-medical sciences with an interest in health information management and quality management, and
- a professor in hospital pharmacy and practical pharmacotherapy.

We assumed we were well informed about the general in-hospital work processes and those regarding the use of the CPOE. One could suspect bias and question the independence of these highly involved researchers. We argue however, that we performed scientific sound research because of, instead of despite, our involvement. We used our knowledge to carefully select differing (surgical and nonsurgical) specialties for the qualitative studies, but for the quantitative

studies we included all overrides to grasp any unanticipated differences. Furthermore, the selection of orders for the functionality and simulation tests was successful because of a thorough knowledge of alert types and familiarity of alerts and insight into the Dutch drug database. The scientific analysis of our data and the results obtained surprised us several times, making bias unlikely. For example we assumed that potassium serum levels were being measured routinely, that physicians would agree to turning several DDIs off hospital-wide, that nurses were awaiting the opportunity to adjust drug administration times themselves and that cardiologists were regularly evaluating QTc intervals, but none of these assumptions appeared to be completely true. The hospital appeared to be a complex sociotechnical system in which the use of the CPOE was dependent on local circumstances such as work routines, knowledge, and culture [3] that varied between specialties. The different backgrounds in our research group subsequently helped us to explain unanticipated results. In this thesis we have shown that succesful research in the complex sociotechnical environment of a hospital is feasible with researchers from different specialties.

REASON'S MODEL OF ACCIDENT CAUSATION APPLIED TO DRUG SAFETY ALERTING

In chapter 2.1 we applied Reason's model of accident causation to drug safety alerting and used this model to interpret how an alerting system designed to prevent errors may provoke them (Figure 2). The different error-producing and latent conditions in software and organization presented in this model came up for discussion in the rest of the chapters. This poses the question whether this model was useful for understanding the problems of safety alert overriding in the studies described in this thesis, whether the model requires adjustment, or should be discarded.

We consecutively discuss whether error-producing conditions of the CPOE system, the task and the team were present, and subsequently discuss the latent conditions. In the next section on unraveling alert fatigue, individual error-producing conditions, active failures and a model adjustment are discussed.

Error-producing conditions

Information content unclear

In several studies described in this thesis, the information content of the alert text appeared to be problematic. In chapter 3.1 respondents spontaneously commented on text length, sequence and content of the alerts, although turning off was the focus of the study. In chapter 3.3 and 3.4, the most relevant information for alert handling could only be read if the alert text was scrolled down to the bottom. This hampered the preferred handling and possibly

resulted in misinterpretation and in alerts being ignored. On the other hand, a measure aiming at improving the information content, the addition of a level of seriousness indication to the top of the alert text, was indeed perceived useful (chapter 3.2).

We propose the presentation of the alert to also be included in the category 'information content', because the fact that the second alert in one pop-up screen was often overlooked in the simulation test suggests that the information presented was not clear enough to prevent it being overlooked.

Low alert specificity

Low alert specificity also appeared to be very important. The CPOE used in the Erasmus University Medical Center (Medicatie/EVS®) had a specificity of 21% in the functionality test presented in chapter 2.4, which was low compared to other CPOEs. Furthermore, Medicatie/EVS® had no functionality to prevent sequence-dependent DDI alerts and these accounted for 21% of the alert overrides (chapter 2.2). Time-dependent DDI alerts appeared to have low specificity: even correct time intervals resulted in alert generation, due to time indications being absent in the Dutch drug database. QT-prolongation alerts showed low specificity because alert generation did not take into account non-drug-related risk factors such as age, electrolyte levels, comorbidity and renal function.

Low sensitivity

Low sensitivity was not found to be a major problem of Medicatie/EVS® in this thesis, although hospital pharmacists clearly missed functionality for contraindications, allergies and for dose regimens less frequent than once a day. These functionalities appeared to be present in other hospital CPOEs, suggesting that it would be feasible to introduce them. In chapters 3.1 and 3.5 the effects on sensitivity were reasons not to implement the proposed measures.

Handling inefficient and unsafe

Inefficient and unsafe handling was clearly present in the case of time-dependent DDIs: orders had to be confirmed and adjusted afterwards, and this easily forgettable step was error prone (chapter 3.3). The fact that ECGs could not be ordered directly from the CPOE was also inefficient, and might have been a reason for the low proportion of QT alerts resulting in ECG recordings (chapter 3.4). The same is true for DDIs that ought to have been monitored by measuring serum levels and that could not be ordered directly from the CPOE.

Workflow unnecessarily disrupted

We perceived the low-specificity time-dependent DDIs (TDDIs) as alerts unnecessarily disrupting physicians' workflow and thus candidates for handling by nurses. Medical coordinators and head nurses however preferred TDDIs to be handled (correctly) by physicians. Although TDDIs were present in the top 20 of most frequently overridden drug safety alerts, the number of

TDDIs was on average not very high (6.2 per day on 28 wards) and was perhaps not bothering physicians too much.

Latent conditions

Turning off alerts

Turning off drug safety alerts can result in low sensitivity if performed without adequate error management. Many respondents in the interviews about turning off alerts (chapter 3.1) feared that hospital-wide alert suppression would result in (preventable) errors. They perceived the reduction in sensitivity as a situation thwarting patient safety. In chapter 3.5, a single alert was turned off nationally for several drugs and resulted in low sensitivity that hospital pharmacists deemed unacceptable.

Trust in (absent) pharmacy check

The simulation study described in chapter 2.3 revealed that physicians often ignored alerts because they trusted in alert handling formerly performed by other people. In the model we only described 'trust in (absent) pharmacy check', but 'trust in other physicians' was mentioned far more in this study. These results show that medical work indeed is a collective, highly collaborative process building on (previous) decisions by other people. We therefore suggest changing this box to 'Trust in checks by other people', which could include previous decisions by physicians or (community) pharmacists, as well as daily checks of overridden alerts by hospital pharmacists.

Trust in, or dependency on, alerting system

There were some signs of 'trust in or dependency on alerting system' resulting in wrong selections, but the majority of physicians following alert recommendations mentioned they would check later with other sources of information.

Insufficient training

The simulation study also suggested that 'insufficient training' played a role in misinterpretation of alerts, because physicians, especially surgical residents, often were using incorrect rules to justify overriding. For example, they referred to monitoring of drug serum levels that were inappropriate for the alert at hand. The unclear content of the alerts did not help to solve this problem.

Conclusion

In conclusion, the model presented in chapter 2.1 appeared to be helpful for understanding and applicable to the CPOE used in Erasmus MC. The error-producing conditions appeared to be more clearly present than the latent conditions, which was as expected as the latter are

more diffuse in origin. Low specificity, unclear information and inefficient and unsafe handling were the most important error-producing conditions. The latent condition 'Trust in (absent) pharmacy check' should be replaced by 'Trust in checks by other people'.

UNRAVELING ALERT FATIGUE

In chapter 2 of this thesis, we tried to unravel the problem of alert fatigue. We wanted to know whether alert fatigue was present in our hospital, and which determinants played a role. Research on this topic appeared to be absent and we could find only one defintion of alert fatigue. Peterson defines it as the mental state that is the result of too many alerts consuming time and mental energy, which can cause important alerts to be ignored along with clinically unimportant ones [4]. Operationalization of the concept of alert fatigue into parameters that can be measured was absent.

Definition of alert fatigue

Fatigue, which can be both physical and mental, is defined as 'weariness caused by exertion', and is also described as exhaustion, lethargy, languidness, languor, lassitude and listlesness. Mental fatigue can manifest itself as a general decrease of attention, and/or somnolence [5]. Peterson defines alert fatigue as 'the mental state', thereby indicating that it is a form of mental fatigue. He describes the cause of this type of fatigue (too many alerts consuming time and mental energy), and also defines the consequences (important alerts being ignored along with clinically unimportant ones). Peterson defines the cause of alert fatigue as 'too many alerts consuming time and mental energy', but the number of alerts was said to be less important than the signal-to-noise ratio [6]. We therefore propose rewording it to 'alerts consuming too much time and mental energy' so including both the number and the characteristics of the alerts. Furthermore, ignoring suggests that alerts are completely disregarded. If mental fatigue manifests itself as decreased attention however, misinterpretation and wrong selection should also be included in the definition of alert fatigue. Overriding without paying sufficient attention to the alert was shown to be more prevalent than completely ignoring alerts. In chapter 2.1 we argued that only 'unjustified' overriding poses a problem in contrast to overriding per se. We use the term 'unjustified' instead of 'erroneous', because the overriding may be accidentally correct and unjustified at the same time. This appears to be the case if rules that are incorrect itself or not applicable in the situation at hand, are applied because of decreased attention. We therefore propose to redefine alert fatigue as 'the mental state that is the result of alerts consuming too much time and mental energy, which can cause relevant alerts to be unjustifiably overridden along with clinically irrelevant ones'.

Model adjustment

This new definition has consequences for the model of accident causation. Lack of motivation and alert fatigue were both put in one box as individual error-producing conditions that result in ignoring alerts. As fatigue includes listlessness, this lack of motivation is already included in the term alert fatigue and can be removed from the box. Furthermore, this box should not only point at 'ignoring alerts', but also to the other active failures: 'misinterpretation' and 'wrong selection'. As alert fatigue is the result of 'alerts consuming too much time and energy', the box 'lack of time' should also point at 'alert fatigue'. These changes result in the adjusted model presented in Figure 3.

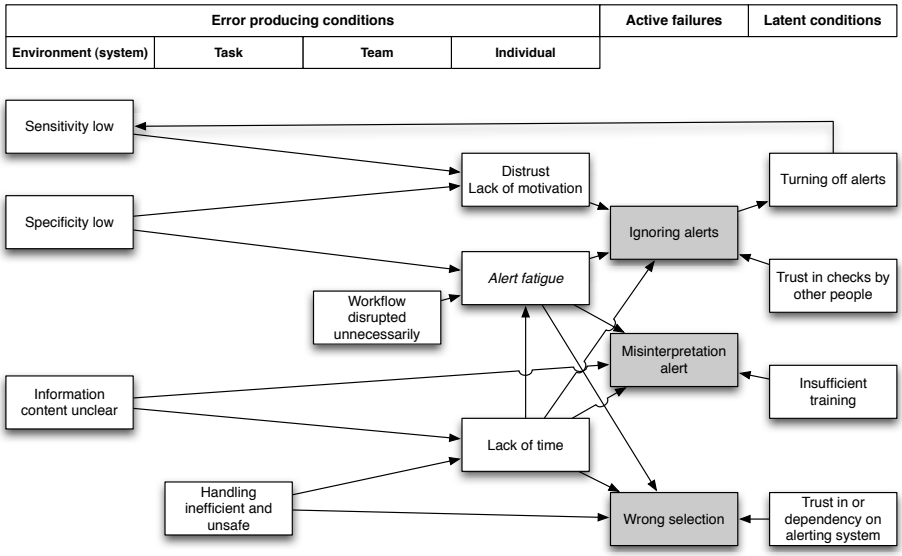

Figure 3 Adjusted model of accident causation applied to drug safety alerts in CPOE

Operationalization of alert fatigue

This new definition of alert fatigue has several starting points for operationalization. Alert fatigue should in our opinion be measured as follows: a high alert generation rate, a high override rate, physicians complaining about several error-producing conditions such as low alert specificity, unclear information content, inefficient alert handling or alerts unnecessarily disrupting their workflow. Measurable consequences of alert fatigue are physicians (mentioning) ignoring alerts and overrides of clinically important alerts that physicians cannot justify or cannot be justified by an expert panel.

Quantitative aspects

In chapter 2.2 we showed that 34% of orders generated an alert on internal medicine wards. It is not clear whether one-third of orders generating an alert should be perceived as high. Other

CPOEs showed lower alert generation rates of 7% to 30% [7-11], but comparisons are difficult because of functionality differences. The higher percentages refer to CPOEs with more comprehensive drug safety alert functionality. As the alert number was said to be less important than the importance of the alert [6], override rates possibly are more important.

On internal medicine wards, we measured an overall override rate of 91%, which is said to be high [12], but which has been observed in other CPOEs as well: 90% and 94% in the studies of Nightingale and Weingart respectively [8,13]. Bates proposed a much lower override rate of less than 40% for strongly action-oriented suggestions [14]. It is not clear however if the overridden alerts in our study belong to this category or how this percentage came about as it appears to have been chosen arbitrarily [14]. Overriding does not necessarily mean that the alert is useless, the physician might have been triggered to reconsider the benefit-risk ratio, to initiate or increase patient monitoring, or to inform the patient about symptoms that should be reported. In this thesis, the latter actions were not taken into account to calculate such a 'clean' override rate, which would be lower.

Because annulled alerts were not logged in Medicatie/EVS®, the alert generation rate and override rate could only be revealed using disguised observation in the field setting. This observation was time consuming, could only be performed for internal medicine wards and could not be extrapolated to other specialties or hospitals. To get an insight into overriding, we therefore often used the number of overridden alerts per prescribed order in this thesis. Our measured percentage of 20% could have been obtained with an alert generation rate of 22% and an override rate of 90%, but could also point to a much higher alert percentage of 44% consuming far more time and energy for alert handling, with an override rate of 45%. Absence of logging of generated alerts hampered interpretation of quantitative results in both chapters 2.2 and 3.2. We therefore argue that CPOEs should log generated alerts that are annulled as well as all those resulting in overriding to enable this part of alert fatigue to be monitored quantitatively.

Qualitative aspects

Besides these quantitative measures, alert fatigue was also observed in the qualitative parts of the studies. Several respondents in the study on turning off frequently overridden alerts in chapter 3.1 complained about content, sequence and length of the alert texts. The fact that 48% of the respondents in chapter 3.2 had not noticed the addition of the level of seriousness implies that alert texts are not read and this further supports the presence of alert fatigue.

Regarding the second part of the definition of alert fatigue, the consequences of alerts consuming too much time and energy were clearly shown in the simulation test of chapter 2.3. Respondents mentioned they were 'completely overwhelmed by the alerts', 'often inclined to rapidly click them away', or said they 'simply skipped them'. Furthermore, residents who overrode an alert sometimes said they really had not noticed it. This overriding without paying attention to the alerts is a symptom of alert fatigue. The expert panel analyzing override reasons

often categorized these as unjustified, because of incorrect rules or reasoning. The majority of alerts were not given much attention and the low specificity of the alerts was often mentioned. Chapter 3.4 showed that even the clinically important QT prolongation alerts were overridden frequently without the preferred action of recording an ECG.

Individual differences

Although alert fatigue appeared to be clearly present, we discovered also that not all physicians suffered from alert fatigue. Several respondents in chapter 3.1 did not want to turn off any alerts because alerts did not bother them. In the simulation study, one respondent complained about the CPOE but perceived the drug safety alerting as a positive feature. Like fatigue in general, alert fatigue appears to be individually dependent. This does not imply that those complaining should stop whining and fit themselves in their surroundings. The physician should not be blamed for making active failures that the drug safety alerting system provokes. The studies in the first part of this thesis have shown that several starting points for improvement are present in the drug safety alerting system.

COUNTERACTING ALERT FATIGUE

In chapter 3 we tried to decrease the burden of excessive numbers of DDIs in four different ways. We examined ways of turning off alerts and changing information content, workflow and specificity, but it appeared to be very difficult to counteract alert fatigue. Although we were not very successful in counteracting alert fatigue, our approach to addressing different error-producing and latent conditions generated a lot of ideas for future improvements. In this section we discuss the different attempts, why we thought these would be successful, and why this was not the case. Subsequently, we present a roadmap for improvement.

Turning off frequently overridden alerts

In chapter 3.1 we studied whether frequently overridden drug-drug interactions could be safely turned off hospital-wide. We hypothesized that several alerts become irrelevant in a hospital setting where drug serum levels or clinical effect-related patient parameters are monitored routinely. Turning off these irrelevant alerts for inpatients would then reduce the number of DDI alerts and the mental energy required. Twenty-four frequently overridden alerts were presented individually to 18 physicians of different specialties and 6 pharmacists. We asked whether these could be safely turned off hospital-wide and requested reasons for the decisions. We expected considerable agreement among the respondents that alerts with a low level of seriousness and alerts recommending routine monitoring should be suppressed. However, there were no alerts that all clinicians agreed could be turned off safely. Several respondents mentioned that residents and surgeons should continue receiving alerts because of their

limited drug-related knowledge and negligence of ordering clinical chemistry measurements such as potassium and creatinin. This suggested that turning off alerts hospital-wide is not feasible. An alternative would be knowledge-specific or specialty-specific alert suppression or nonintrusive alert presentation.

Adding levels of seriousness to the alert text

In the next chapter (chapter 3.2) we focused on the information content of the alert, because content, sequence and length often attracted negative comment. A level of seriousness was absent in the alert and we hypothesized that a clear presentation of it (in capitals at the top of the alert text) would help physicians in their alert handling. We expected a decrease in high-level overrides and increased overriding of low-level alerts, without changing the overall override rate. However, we elicited an unexpected increase in override rate for all levels of seriousness. Physicians who overrode alerts and were sent a questionnaire about the new alert texts replied that this extra information on level of seriousness was useful for alert handling. With these qualitative results we drew the conclusion that the level of seriousness information reduced the mental time and energy required for alert handling and should continue to be shown to the users. The increased override rate possibly did not imply increased ignoring (and alert fatigue), as overriding might have been justified by increased monitoring or other appropriate responses not resulting in annulment.

Directing alerts to other people in the workflow

In chapter 3.3 we studied whether alerts regarding drug administration time could be directed to nurses to decrease the burden of excessive alerts shown to the physician. As nurses generally administer drugs to patients, we hypothesized them to be the key persons to handle DDIs related to drug administration times. We discovered that nurses frequently corrected physicians' prescribing errors arising from incorrectly handled time-dependent DDIs (TDDIs). We were therefore surprised that medical coordinators and head nurses did not agree with our proposal to let nurses handle these alerts and that they preferred physicians to handle them. As feedback from pharmacy technicians did not result in a reduction in administration errors and percentages of prescribing errors remained high (79-87% of all TDDIs), we examined the handling of TDDIs in greater detail. We discovered several imperfections in the alert generation, presentation and handling that hampered drug administration error reduction. The most relevant part of the alert text, with the recommendation to administer the drugs with a time interval, could not be seen at first glance, but only when scrolled down to the bottom. Furthermore, adjusting the time interval was inefficient and error prone. If the physician prescribed the time interval correctly following the alert, a TDDI alert was generated again. So low specificity, unclear information, and inefficient handling of TDDI alerts hampered correct prescribing and increased the risk of alert fatigue.

Increasing specificity

Chapter 3.4 and 3.5 addressed the frequently overridden alerts on QT prolongation. We discovered that the preferred response to these alerts, to request an electrocardiogram (ECG), was rare. As in chapter 3.3 we discovered that unclear information and inefficient handling inhibited the correct response. Furthermore, alert generation was not tailored to female gender, older age, low potassium serum levels and bad renal function, and did not take into account comorbidity or drug dose.

Chapter 3.5 describes a study to assess the effect of a proposed measure to reduce QT alert overload by increasing specificity of the QT alerts. The Dutch drug database, which is used as the knowledge base in Medicatie/EVS®, reduced the number of QT-prolonging drugs by selecting only those drugs that were clinically proven to induce Torsades de Pointes (TdP) in monotherapy and deleting those with a probable risk of developing TdP. Although this measure decreased the number of QT alerts, it did not result in a better positive predictive value of the alerts. Furthermore, several patients at risk of developing TdP were missed with the shortened list, resulting in low sensitivity. These unintended consequences were due to the fact that the effect of two drugs with probable risk of developing TdP and the partial effects of non-drug-related risk factors on the QT interval are unknown.

Conclusions

Although the measures we examined to counteract alert fatigue were not very successful, the studies in this thesis revealed a lot of relevant pointers to future improvements. The major problems hampering reduction of alert fatigue appeared to be the information content of the alerts and missing links between the CPOE and the electronic medical record (EMR). A major problem with the information content was the length of the alert text, requiring scrolling down to the bottom and hampering triage at a glance. Lack of linking with the rest of the EMR hampered alert suppression related to measured serum levels, and correct responses because of absence of ordering for ECGs or lab tests. As many different factors play a role in the development of alert fatigue, it is likely that decreasing the burden of excessive alerts can be achieved only by applying a combination of different methods for improvement, addressing more than one factor.

RECOMMENDATIONS FOR IMPROVEMENT AND FUTURE RESEARCH

In this last section, we discuss which measures to counteract alert fatigue should be tested and how future research should be performed.

Information content

The first successful step in counteracting alert fatigue was to improve alert content by presenting the level of seriousness clearly at the top of the alert text. However such local adjustment requires continuous local maintenance and it would be very helpful if the Dutch drug database could incorporate these seriousness indications in the alert texts. The next step would be to adjust alert texts to enable triage at a glance. Text testing, which is absent now, should be performed by future users before implementation. Furthermore, testing the presentation of these texts in the CPOEs should also be incorporated to ensure that relevant information is indeed shown to the user at first glance. Subsequently, studies should check whether this indeed results in a reduction of the mental energy required for alert handling and in a learning effect.

Increasing specificity

A second step towards improvement should focus on relatively simple measures to increase specificity. Several hospital CPOEs are able to prevent false-positive alerts by using the sequence indications provided by the Dutch drug database. This suggests that this improvement could be achieved rather easily. The possibility of time indications to prevent false-positive time-dependent DDIs should be studied. If the alert recommendation states a required time interval of at least 2 hours, the alert should contain a coded indication for the 2-hour interval that would enable alert suppression if the time interval is already correct.

Linking with the electronic medical record

Drug safety alerting should be further improved by linking the CPOE and laboratory systems first outside and later during the order entry process. Linking them outside the order entry process can be used to check whether serum levels are indeed being measured and are staying within limits. It is unknown whether serum level measurements are alert-triggered or routinely performed. If alerts are turned off or shown nonintrusively the CPOE-lab link can be used to distinguish between these two types.

The next step towards improvement is integration of laboratory results into the medication order entry process, first showing results and enabling ordering, in time implementing intelligent decision support systems. If serum level measurements are required to monitor dosing or for alert handling, the CPOE should indicate whether these have indeed been measured recently, and the results. An ordering option would be very helpful too.

Subsequently, this CPOE-laboratory link could be used for intelligent decision support systems for suppressing or generating alerts, for example suppressing alerts warning of rising potassium levels if the potassium level is low. A similar link between CPOE and EMR should be developed for electrocardiogram presentation, ordering and integration into clinical rules. The development of a clinical rule for QT prolongation with an acceptable positive predictive value is challenging, as comorbidity information would also need to be obtained from the electronic

medical record; this could possibly be achieved by data mining. All adjustments should be monitored for reduction of alert fatigue and unanticipated (adverse) effects.

Other avenues for future research

Other unanswered research questions are:

1. Do nonintrusive alerts prevent adverse events as well as alert fatigue?
2. What is the effect of a mandatory field for entering override reasons on alert fatigue?
3. Does changing the default configuration from 'override and confirm order' into 'adjust order' for DDIs and duplicate orders result in decreasing numbers of (unjustified) overrides?
4. What is the best way of presenting multiple alerts for one medication order to prevent oversight?
5. How should over- and underdoses be best shown to the user for easy understanding?
6. What is the specificity of the newer functionalities in the Dutch drug database that are presented as a form of contraindication but mainly require dose adjustment (impaired renal function, impaired liver function, pharmacogenetics).
7. Is an overview of all drug safety alerts of a patient in one screen helpful for physicians or pharmacists?

Health information management deals first and foremost with the challenge of integrating health information systems into health care work in such a way that the quality of that work is improved [15]. In this thesis, we have shown that improvement is difficult to achieve. The role of information technology in healthcare is growing and this affects the tightly interwoven roles and tasks of health care professionals and their environments. At first glance it looks simple to improve a CPOE, but in this thesis we have shown that it is not.

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Chapter 5

Summary and Conclusions

INTRODUCTION

In modern healthcare, prescribing drugs is one of the forms of medical treatment most frequently used. The medication process consists of different phases: drug prescribing, dispensing and administration, and errors may occur in every phase of this process. An important measure to reduce medication errors is prescribing drugs electronically using a computerized physician order entry system (CPOE). Computerized physician order entry (CPOE) systems frequently include integrated decision support components, which can improve patient safety. Studies documenting positive effects of decision support on patient outcomes have prompted calls for additional patient-specific advice. On the other hand, if the burden of alerts is too high, alert fatigue may cause physicians to override both important and unimportant alerts, in a manner that compromises the desired safety effect of integrating decision support into CPOE.

Alert fatigue is a poorly-understood phenomenon. The aim of this thesis was to gain an insight into drug safety alert generation and overriding and to decrease the burden of excessive numbers of drug safety alerts, in an attempt to understand and counteract alert fatigue. In this chapter we summarize the findings and draw conclusions.

INSIGHT IN GENERATION AND HANDLING OF DRUG SAFETY ALERTS

In chapter 2 we focus on unraveling alert fatigue. In **chapter 2.1** we describe a literature study on physician response to drug safety alerts. Only 17 papers met our inclusion criteria. Clinicians overrode drug safety alerts in 49-96% of cases. Overriding should not be perceived as a problem in itself, it might be justified in the event of non-specific or incorrect alerts. Frequent overriding however may result in alert fatigue, which is described as the mental state that results from too many alerts consuming time and mental energy, which can cause important alerts to be ignored along with clinically unimportant ones. This unjustified overriding should be prevented.

We used Reason's framework of accident causation to interpret how systems generating many safety alerts may provoke errors and hamper patient safety. An alerting system may contain error-producing conditions such as low specificity, low sensitivity, unclear information content, unnecessary workflow disruptions, and unsafe and inefficient handling. These may result in active failures of the physician, such as ignoring alerts, misinterpretation, and incorrect handling. The reasons for and the frequency of these active failures are unknown because studies on the role played by cognitive processes in overriding drug safety alerts are lacking. We designed the simulation study described in chapter 2.3 to gain an insight into this aspect of alert handling.

Efforts to improve patient safety by increasing the correct handling of drug safety alerts should not focus on physicians' errors however, but on the error-producing conditions in software and organization that cause these active failures.

In the following two chapters we report physicians' behavior in handling drug safety alerts in daily practice of a large Dutch University Medical Center (**chapter 2.2**) and in a laboratory session (chapter 2.3) using the CPOE Medicatie/EVS® from iSOFT (Leiden, the Netherlands). This CPOE generates drug safety alerts for drug-drug interactions (DDIs), overdoses and duplicate orders, which are presented intrusively (as pop-up screens) to the user. Overridden alerts are logged for pharmacy checking. However, alerts that are annulled (by the physician cancelling or adjusting orders) are not logged and are therefore not available for retrospective analysis.

To gain an insight into the number of alerts generated and annulled we performed a disguised observation study. We told 6 residents in internal medicine that we wanted to study CPOE use for possible improvements and observed alert generation and handling over 5 weeks during normal day shifts. Thirty-four percent of the 515 orders generated a drug safety alert, of which 91% were overridden. The majority of alerts generated (56%) concerned drug-drug interactions (DDIs) and these were overridden more often (98%) than overdoses (89%) or duplicate orders (80%). In addition to the disguised observation study we performed a retrospective analysis of all drug safety alerts overridden in a two-year period. Twenty percent of the prescribed orders resulted in an alert override and DDI overrides were most abundant (59%). In 36% of DDI overrides, the effects could be monitored by clinical chemistry data or drug serum levels. The top 20 of overridden DDIs accounted for 76% of all DDI overrides.

These studies on overriding in daily practice showed that DDIs were overridden most commonly and that only a small number of DDIs were responsible for these overrides. This suggested that low specificity might have been a problem for these alerts. Studies on improvement of alert handling should focus on these frequently overridden DDIs.

Although the abovementioned studies gave an insight into the number and type of alerts overridden, it did not address why alerts are overridden or annulled, which cognitive processes play a role and which errors are made. This was the topic of **chapter 2.3**.

We told residents willing to participate (12 from internal medicine and 6 from surgery) that we were studying the user friendliness of the CPOE, and did not disclose the real goal of studying alert handling. We designed a laboratory study with 6 patient cases and 13 different known and unknown alerts. After a patient handover the resident was asked to enter the 36 orders from the patient cases in a noisy atmosphere under time pressure, thereby simulating their normal work environment. Alert handling was recorded on an observation form and used for an interview about reasons for the performed handling. This took place directly after the test was completed.

Thirty percent of alerts were handled incorrectly, because the action itself (24%) and/or the reason for the handling (16%) were incorrect. Sixty-three percent of the errors was handled with internalized rules of the type 'if-then' and residents in surgery used incorrect justifications twice as often as residents in internal medicine. They overrode or annulled alerts correctly by using wrong rules, or by rules not applicable to the situation in 13% of cases (internal medicine 5%). They often referred to monitoring of incorrect substances or parameters. In several CPOEs the override reason 'patient being monitored' can be selected from a dropdown box and pharmacists perceive this as useful for order verification. Our findings suggest the reason 'patient being monitored' is insufficient to prevent error and should ideally be accompanied by clinical rules checking for correct serum levels, ECG recordings, and blood pressure measurements.

Misinterpretation was rife and therefore, unambiguous, concise, and easy-to-understand alert texts are recommended. One alert presented as a second alert in one screen was unconsciously overridden several times. Usability studies are necessary to investigate how alerts should be presented to prevent oversight. One quarter of residents was judged to suffer from alert fatigue, mainly because of low-specificity DDI alerts. They were overwhelmed by the high numbers of alerts and admitted to simply clicking them away. Increasing specificity is therefore proposed as a major improvement measure.

The quality of drug safety alerting in different CPOEs used in Dutch hospitals was the topic of **chapter 2.4.** Quality was defined as the ability to generate alerts in potentially unsafe situations (sensitivity), and to prevent alert generation in safe situations (specificity). Quality is dependent on the knowledge base used, functionality of the CPOE and local configurations and knowledge base adjustments. In the Netherlands all hospital CPOEs use the Dutch national drug database as the knowledge base for drug safety alerting. This G-standard contains safety information for all medicines licensed in the Netherlands.

We designed a test with 29 test items for sensitivity and 19 for specificity, which was mainly based on the G-standard. In the sensitivity test alerts should be generated and in the specificity alerts should remain absent. We performed this test on 6 different hospital CPOEs (used in 98% of the Dutch hospitals with a CPOE) in the offices of the CPOE system vendors, to control for any local adjustments.

Our test revealed widely varying functionality despite a common knowledge base. Sensitivity ranged from 0.38 to 0.79 (38% to 79% of the test items resulted in an alert) and specificity from 0.11 to 0.84 (in 11% to 84% of the test items the alert was correctly absent). The test appeared to be highly discriminative. The systems achieved the same ranking for sensitivity and specificity, which suggested that the vendors of the best-performing CPOEs tried to introduce new functionality as soon as it became available while other CPOE vendors awaited requests for new functionality from health care providers. Within-order checks and patient-specific checks were present in all systems; alert generation or suppression due to laboratory data and new patient conditions were largely absent.

To interpret these results, we performed qualitative interviews with 16 hospital pharmacists evaluating their perceived importance of missing functionality and corresponding pharmacy checks to address it. Hospital pharmacists unanimously rated checks on contraindications (absent in 2 CPOEs) and dose regimens less frequent than once a day (absent in 4 CPOEs) as important. Pharmacists' opinions were more divergent for other test items. A variety of pharmacy checks were used, and clinical rules were developed, to accommodate the lacking functionality.

The CPOE Medicatie/EVS® used in the other studies of this thesis had a low specificity of 21%, which explains the observed signs of alert fatigue. On the other hand, this low value as compared to the best performing Dutch hospital CPOE (84%), suggests that improvement is feasible.

DECREASING THE BURDEN OF EXCESSIVE NUMBERS OF DRUG SAFETY ALERTS

In chapter 3 of this thesis we focused on measures to decrease the burden of excessive drug-drug interaction (DDI) alerts. In the Dutch drug database (G-standard) combinations of drugs mentioned in the literature as DDIs are categorized as yes/yes (interacting and requiring action), yes/no (interacting but requiring no action), and no/no (not interacting, requiring no action). Furthermore, almost all DDIs have been assigned an alphanumeric code combining an evidence (from zero to four) and seriousness index (from A to F). The G-standard also provides standard alert texts. In the CPOE Medicatie/EVS® used in the Erasmus University Medical Center, only yes/yes DDIs are generated, presenting the national alert text. The alphanumeric code is not shown to the user.

We first studied measures aiming at better usability for the physician. In **chapter 3.1** we report on whether frequently overridden DDIs could be safely turned off hospital-wide, to reduce alert overload. We selected alerts overridden more than 10 times in one month. DDIs without an alphanumeric code were excluded because seriousness was thought to be an important consideration in specialists' decision whether to turn off. DDIs concerning drug administration time were excluded as well because it was proposed to direct these alerts to other people in the workflow (which is described in chapter 3.3). We presented screen shots and complete texts to 18 physicians from internal medicine, cardiology and surgery and 6 hospital pharmacists and asked them whether these alerts could be turned off hospital-wide without impairing patient safety, and the reasons for their recommendations.

Although only yes/yes DDI alerts, requiring action, were included, the majority of respondents wanted to turn off alerts. However, for none of the alerts did all respondents agree that it could be safely turned off hospital-wide and the highest agreement was 13 of 24 respondents

(54%). A quarter of respondents recommended not turning off any alerts hospital-wide, either because the alerts did not bother them (suggesting that perceived data overload is individual dependent), or because they feared that a perceived lack of knowledge among residents and surgeons would lead to errors that alerts could prevent. Furthermore, routine drug and electrolyte monitoring practices appeared to differ across the hospital. Therefore, turning off alerts hospital-wide appeared to be problematic.

Besides disagreement in the recommendations to turn off, many differences in the reasons for turning off alerts were found across medical specialties and among respondents within a specialty. Frequently mentioned reasons for turning off were 'alert well known', 'alert not serious' or 'alert not needing (additional) action', or that the effects of the combination were being monitored or were intended.

Several reasons for suppressing alerts were questionable from a safety perspective, such as 'effects intended' (may not be the case for all specialties), 'only prescribed by specialists' (may be accidentally prescribed), 'no action needed' (all alerts were categorized as requiring action) or 'alert well known' (lack of attention, distraction and forgetfulness are known to frequently cause errors).

The number of alerts overridden and the number of clinicians recommending turning them off were positively correlated, although respondents hardly mentioned the number of alerts as a reason for alert suppression. Respondents spontaneously gave negative comments on the information content, sequence and length of the national alert texts.

This study suggested generating or suppressing alerts based on clinician knowledge or specialty, and distinguishing between important alerts presented as pop-ups and less relevant alerts that could be shown nonintrusively. Furthermore, we hypothesized that changing the alert texts might help reduce alert fatigue by decreasing the mental energy needed for alert handling.

In **chapter 3.2** we describe the effects of such a change in the alert text. We added a description of the level of seriousness and the alphanumeric code in capitals to the top of the alert text and studied whether the overrides per prescribed order changed as a whole and per level of seriousness.

The percentage of overrides per prescribed order increased statistically significantly from 10.8% to 12.8% after the level of seriousness was added to the alert text (18%, $p<0.001$). Increases in the number of overrides per prescribed order were observed for all levels of seriousness and was highest for the medium-level alerts (24.8%), followed by low (12.3%) and high-level (6.2%) alerts.

We also asked sixty-nine different physicians who overrode DDI alerts whether the addition of the level of seriousness was helpful. 42 physicians responded and 62% of them perceived this information as useful for alert handling, although they did not use the alphanumeric code.

The increased overriding does not imply that alerts are ignored to a larger extent due to alert fatigue, because the increased overriding may be accompanied and justified by increased patient monitoring. The majority of respondents perceived the additional information on seriousness as helpful, suggesting a decrease in the burden of excessive alerting on the physician, and in the risk of alert fatigue.

In the latter part of chapter 3 we describe patient risk due to overridden alerts. In **chapter 3.3** we report on overridden time-dependent drug-drug interaction alerts (TDDIs). Chapter 2.2 showed that these alerts, indicating that a time interval between administering different drugs is required, are frequently overridden. Our objective was to reduce drug administration errors due to overridden TDDIs. We studied overridden TDDIs by comparing the time intervals prescribed in the CPOE and those recorded on the patient chart. Although written and verbal education resulted in a statistically significant administration error reduction from 56.4% to 36.2%, the percentage prescribing errors remained high (79-87% of all TDDIs).

Several imperfections hampered correct prescribing and helped explain the lack of reduction in drug administration errors. The handling of the TDDI alerts appeared to be inefficient and error prone because the order had to be cancelled and prescribed again, or it first had to be confirmed and adjusted afterwards. The preferred option, to adjust the new order, was absent. If the physician then prescribed the correct time interval, a TDDI was generated again because time indications were not used in alert generation. Consequently alert specificity was low. Furthermore, the most relevant part of the alert text (recommending time interval and sequence of administration) could only be read if it was scrolled down. To enable alerts to be handled correctly by physicians (and administration errors to be reduced) the alert texts in the G-standard should be adjusted and time indications included. CPOE systems should be improved to include an 'adjust order' button and functionality for using time indications.

Other frequently overridden alerts present in the top 20 from chapter 2.2 were alerts on QT prolongation. Prolongation of the QT interval on the electrocardiogram (ECG) may predispose to fatal ventricular arrhythmias, such as Torsades de Pointes (TdP). A linear relationship between QT prolongation and risk of TdP is absent but a patient with a QTc interval longer than 500 ms (millisecond), or whose QTc interval increases by more than 60 ms from baseline, is regarded to be at risk of TdP. Risk factors for QT prolongation are long QT syndrome, older age, female gender, cardiovascular disease, bradycardia, and electrolyte disturbances. Furthermore, several drugs may result in QT prolongation either if potassium currents are blocked and/or if serum levels of these drugs are raised by DDIs that reduce cytochrome P450 activity. Higher doses and renal failure may also result in higher serum levels of these drugs and consequently in QT prolongation. Consequently, the combination of two or more QT-prolonging drugs requires an ECG to assess the QT interval.

In **chapter 3.4** we report on our investigation whether the physician had requested an ECG in patients for whom QT alerts were overridden and if these ECGs showed clinically relevant QT prolongation. For six months we selected inpatients with overridden DDI alerts that might result in QT prolongation if they did not have a ventricular pacemaker and were not taking the low-risk combination of cotrimoxazole and tacrolimus. For the 168 patients who met the inclusion criteria, data on risk factors for QT prolongation, drug class and ECGs were collected from the medical record. In 33% of all patients with overridden QT alerts an ECG was recorded within one month. ECGs were more often recorded in patients with more risk factors for QT prolongation and with more QT overrides. It was not clear however whether ECGs were made because of cardiovascular comorbidity or because of the QT alert. The percentage of ECGs performed due to the alert only might even have been lower than 33%.

Similar problems to those presented in chapter 3.3 played a role: the alert text, handling, as well as specificity appeared to provoke errors. A recommendation to perform an ECG was lacking at the start of the alert text and could only be read if the alert text was scrolled down. If the user decided to request an ECG, the CPOE did not provide a way to order it electronically. Alert specificity, determined by relevance, urgency, and accuracy, was low. The alerts on QT prolongation were relevant because serious arrhythmias might result from overriding, they were urgent because the action of performing an ECG was required, but they lacked accuracy. Alert generation was not tailored to female gender, older age, low potassium serum levels and bad renal function, and did not take into account comorbidity (cardiovascular disease, diabetes mellitus) or drug dose. A link with laboratory data and the patient's clinical information is necessary to increase specificity.

ECGs before and after the QT override were available in 29% of the patients. 31% of the patients in this group showed clinically relevant QTc prolongation with increased risk of TdP. The changes in the QTc interval in these cases were more pronounced than in a control group taking one QT-prolonging drug.

The low proportion of patients in whom an ECG was recorded following the alert, and the high prevalence of clinically important QTc prolongation in patients in whom ECGs were done, suggests patients were at risk. Prescribing physicians should receive more information on the necessity of checking QT intervals after initiating combinations of QT-prolonging drugs, by clear alert texts and by pharmacists reminding them to comply.

After complaints of too many low-specificity QT alerts, the rules for QT alerting in the Dutch national drug database were adjusted. In **chapter 3.5** we discuss whether this adjustment would identify patients at risk of developing TdP better than the old system. We used the study population reported in chapter 3.4 and included the 49 patients with ECGs before and within 1 month of the alert override. QT-interval prolongation and the risk of developing TdP were calculated for all patients and related to the number of patients for which a QT alert would be generated in the new alerting system. In this study population, knowledge base adjustment

would have reduced the number of alerts by 53%. However, the positive predictive value of QT alerts would not change and only 47% of the patients at risk of developing TdP would have been identified by the new alerting system. The adjustment of QT alerting in the Dutch drug database has resulted in a poorer indentification of at-risk patients. Therefore, this new QT alerting has not been introduced in Erasmus University Medical Center.

These unintended consequences are caused by many non-drug-related risk factors for QT prolongation not being incorporated in alert generation. The partial contribution of all risk factors should be studied and used to make clinical rules for QT alerting with an acceptable positive predictive value.

FINAL REMARKS

Reasons' model of accident causation helped us to understand drug safety alerting in computerized physician order entry. It shows that error-producing conditions in software and organization may provoke active failures such as physicians ignoring or misinterpreting alerts, and making wrong selections.

Alert fatigue is the mental state that is the result of alerts consuming too much time and mental energy, which can cause relevant alerts to be unjustifiably overridden along with clinically irrelevant ones. Alert fatigue is induced by alerts with low specificity and unclear information content, alerts unnecessarily disrupting workflow or requiring inefficient handling.

There is much room for improvement, although counteracting alert fatigue is difficult. Adjustments are necessary to the Dutch drug database, the CPOE, as well as the hospital organization. Furthermore, the CPOE and its integrated drug safety alerting are entangled in the social environment in which it is used. Differences in drug-related knowledge, routinely performed measurements and responsibilities may vary between physicians, specialties and hospitals. Hence, adjustments in drug safety alerting should be introduced cautiously and monitored with outcome measurements.

Chapter 6

Appendices

SAMENVATTING VOOR NIET-INGEWIJDEN

Inleiding

In de huidige gezondheidszorg speelt de behandeling met geneesmiddelen een belangrijke rol. De arts schrijft het geneesmiddel voor, de apotheek verstrekt het en daarna dient de verpleegkundige het geneesmiddel toe of neemt de patiënt het zelf in. Zowel bij het voorschrijven, als bij het verstrekken en toedienen of innemen van geneesmiddelen kunnen fouten optreden. Dit noemen we medicatiefouten. Een belangrijke maatregel om medicatiefouten te voorkomen is het voorschrijven van geneesmiddelen met behulp van een elektronisch voorschrijfsysteem op de computer. Medicatiefouten door onleesbare, onvolledige recepten worden voorkomen doordat zo'n elektronisch voorschrijfsysteem alleen leesbare recepten print als de arts alle benodigde gegevens heeft ingevoerd.

Een elektronisch voorschrijfsysteem kan de arts ook ondersteunen in het voorschrijfproces door het genereren van medicatiebewakingsignalen. Deze signalen waarschuwen voor potentieel gevaarlijke situaties en hebben als doel de patiëntveiligheid te vergroten. Als er veel signalen zijn die niet relevant zijn voor de patiënt, bestaat de kans op signaalmoeheid, waarbij artsen niet alleen de onbelangrijke maar ook de belangrijke signalen doorenteren (wegklikken) zonder de juiste actie te ondernemen. Op die manier wordt met de medicatiebewakingsignalen het beoogde veiligheidseffect niet (volledig) gehaald.

Signaalmoeheid was bij de start van onze studie een vrij onbekend fenomeen waar amper onderzoek naar was verricht. Men benoemde het wel, maar het was onduidelijk welke factoren een rol speelden. Het doel van dit proefschrift naar medicatiebewaking in elektronische voorschrijfsystemen was om het fenomeen signaalmoeheid te ontrafelen en tegen te gaan.
We wilden daarom antwoord krijgen op de volgende onderzoeksvragen:

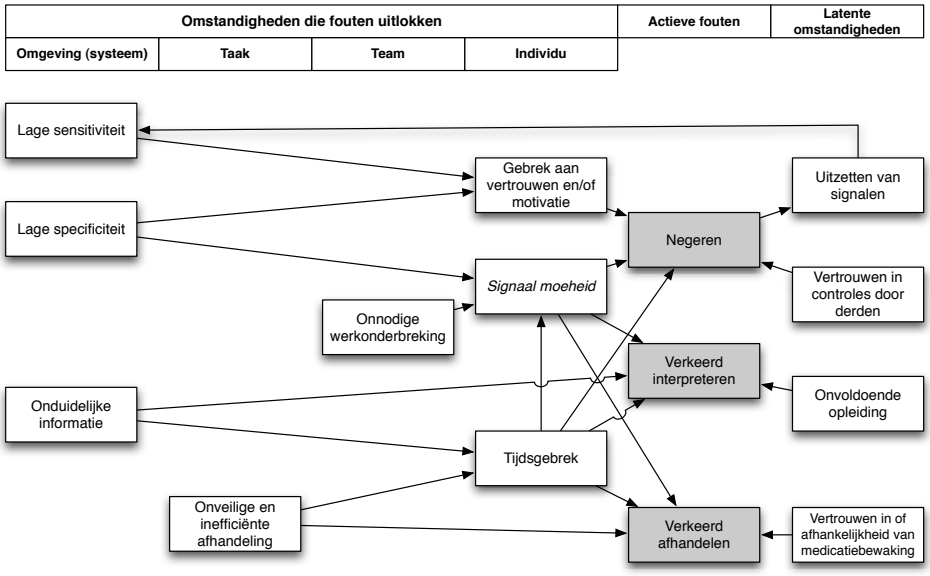
1. Hoe vaak en in welke situaties worden medicatiebewakingsignalen doorgeënterd?
2. Waarom enteren artsen deze signalen door?
3. Welke fouten worden gemaakt bij de afhandeling van medicatiebewakingsignalen?
4. Wat is de kwaliteit van de medicatiebewaking in de elektronische voorschrijfsystemen die in Nederlandse ziekenhuizen worden gebruikt?
5. Kan de last van grote aantallen signalen waarmee de arts wordt geconfronteerd veilig worden verminderd door:
    a. Het uitzetten van frequent doorgeënterde signalen?
    b. Het vermelden van de ernst in de tekst die bij het signaal wordt getoond?
    c. Signalen naar anderen (bijvoorbeeld verpleegkundigen) te sturen?
    d. Signalen specifieker te maken zodat ze meer zijn toegesneden op de patiënt?

In deze samenvatting voor niet-ingewijden beschrijven we in het kort de studies die we hebben verricht, onze bevindingen, het antwoord op de onderzoeksvragen en onze conclusies.
Hoofdstuk 1 is de algemene inleiding op het proefschrift en is hierboven samengevat.

Inzicht in het genereren en afhandelen van medicatiebewakingsignalen

In hoofdstuk 2 beschrijven we hoe we hebben geprobeerd het fenomeen signaalmoeheid te ontrafelen. Eerst zochten we in de literatuur naar artikelen over het doorenteren van medicatiebewakingsignalen. We beschrijven de resultaten van deze literatuurstudie in **hoofdstuk 2.1**. Het bleek dat artsen medicatiebewakingsignalen in meer dan de helft (tot 96%) van de gevallen doorenterden. Het doorenteren kan soms heel goed gerechtvaardigd worden, als de signalen onjuist zijn of niet zijn toegesneden op de patiënt. Het doorenteren op zich hoeft dus niet als probleem te worden beschouwd. Echter, veelvuldig doorenteren kan leiden tot signaalmoeheid waarbij ook belangrijke signalen zonder adequate actie worden doorgeënterd. Dit gebeurt omdat het beoordelen en afhandelen van de signalen teveel tijd en energie kosten. Dit onterechte doorenteren moet worden voorkomen.

Naar aanleiding van de literatuur over doorenteren veronderstelden we dat de oorzaken voor onterecht doorenteren niet (alleen) bij de arts lagen, maar ook in het elektronisch voorschrijfsysteem en de organisatie moesten worden gezocht. James Reason, een Engelse psycholoog, ontwikkelde een model om te begrijpen wat het mechanisme is achter gemaakte fouten en ontstane ongelukken. Hij maakte onderscheid tussen actieve fouten die op de werkplek worden gemaakt en omstandigheden in de organisatie die deze actieve fouten uitlokken. Wij pasten dit algemene model van James Reason toe op de medicatiebewaking in elektronische voorschrijfsystemen. Hierdoor kregen we meer inzicht hoe een systeem met veel medicatiebewakingsignalen de patiëntveiligheid zou kunnen belemmeren in plaats van vergroten. Het model dat we ontwikkelden (Figuur 1) wordt hieronder toegelicht.



Figuur 1 Model van Reason toegepast op medicatiebewaking in elektronische voorschrijfsystemen

Artsen kunnen fouten maken als zij met medicatiebewakingsignalen worden geconfronteerd: ze kunnen ze negeren, verkeerd interpreteren of verkeerd afhandelen. We onderscheidden vijf aspecten van de medicatiebewaking die deze fouten zouden kunnen uitlokken: lage specificiteit, lage sensitiviteit, onduidelijke informatie, onnodige werkonderbrekingen en onveilige en inefficiënte afhandeling. We spreken van lage specificiteit als de signalen niet zijn toegesneden op de patiënt, bijvoorbeeld als bij een geneesmiddel dat aan een man wordt voorgeschreven een signaal komt dat het niet moet worden gebruikt tijdens de zwangerschap. Bij een lage specificiteit krijgt de arts zoveel onbelangrijke signalen dat hij de belangrijke signalen over het hoofd kan gaan zien. Bij een lage sensitiviteit ontbreken waarschuwingssignalen in gevaarlijke situaties, waardoor het vertrouwen van de arts in de medicatiebewaking zo kan dalen dat hij signalen gaat negeren. Als het signaal onduidelijke informatie verschaft over de potentieel gevaarlijke situatie, de ernst en de te ondernemen actie, dan kunnen artsen het verkeerd interpreteren. Ook kunnen zij er zoveel tijd mee kwijt zijn dat ze in tijdnood komen en daardoor fouten gaan maken. Er is sprake van een onnodige werkonderbreking voor de arts als hij een signaal krijgt waar bijvoorbeeld de verpleging iets mee moet doen. Als de arts gemakkelijk op de verkeerde knop drukt of vaak moet klikken, dan valt de afhandeling in de categorie onveilig en inefficiënt.

Naast deze fouten uitlokkende omstandigheden spreekt Reason ook over latente omstandigheden in de organisatie: managementbeslissingen die op een meer indirecte manier kunnen bijdragen aan actieve fouten. Als artsen onvoldoende worden opgeleid, hebben zij mogelijk te weinig kennis om de signalen juist te interpreteren. Zij kunnen het signaal verkeerd afhandelen als zij volledig vertrouwen op het systeem of denken dat de apotheek alles wel zal controleren. Als de apotheek besluit dat sommige medicatiebewakingsignalen uitgezet kunnen worden, dan kan dit de sensitiviteit verlagen en de kans op fouten vergroten.

Het was onbekend hoe vaak de actieve fouten (negeren, verkeerd interpreteren, verkeerd afhandelen) voorkwamen en wat de redenen en oorzaken daarvoor waren. Om dit te onderzoeken, ontwierpen we de simulatiestudie die in hoofdstuk 2.3 wordt beschreven.

We concludeerden dat vergroting van de patiëntveiligheid door juiste afhandeling van medicatiebewakingsignalen niet gericht moest zijn op de fouten die artsen maken, maar op bovengenoemde aspecten van de medicatiebewaking en omstandigheden in de organisatie die deze fouten uitlokken.

In de daarop volgende twee hoofdstukken beschrijven we het gedrag van artsen bij het afhandelen van medicatiebewakingsignalen in de dagelijkse praktijk van een groot academisch ziekenhuis (**hoofdstuk 2.2**) en in een laboratoriumomgeving die de dagelijkse praktijk nabootst (hoofdstuk 2.3). We gebruikten hiervoor het elektronisch voorschrijfsysteem Medicatie/EVS® van de firma iSOFT uit Leiden, dat vroeger Medicator werd genoemd. Dit elektronisch voorschrijfsysteem genereert medicatiebewakingsignalen voor overdoseringen, dubbelmedicatie en interacties. Het geeft de arts een waarschuwing als de voorgeschreven dosering hoger is

dan gebruikelijk (overdosering), als twee geneesmiddelen met dezelfde werking worden voorgeschreven (dubbelmedicatie) of als geneesmiddelen elkaars werking beïnvloeden (interactie). De signalen worden getoond als een 'pop-up': een schermpje met informatie dat het werkproces onderbreekt en pas verdwijnt als de arts een keuze maakt uit de geboden opties: het voorschrift aanpassen of annuleren of het voorschrift ongewijzigd vastleggen (doorenteren). De doorgeënterde signalen worden weggeschreven naar een bestand zodat de apotheek deze later kan controleren. Als de arts het voorschrift direct aanpast of annuleert en het signaal niet meer van toepassing is, wordt het signaal niet weggeschreven naar dat bestand en is het achteraf ook niet meer te raadplegen.

Uit de signaalbestanden is dus niet te achterhalen hoeveel signalen er gegenereerd zijn en hoeveel hebben geleid tot annulering en aanpassing van geneesmiddelvoorschriften. Om daar een indruk van te verkrijgen hebben wij 6 arts-assistenten van interne geneeskunde geobserveerd tijdens het elektronisch voorschrijven van geneesmiddelen. Om te voorkomen dat artsen medicatiebewakingsignalen anders dan normaal zouden afhandelen, hielden we het precieze doel van onze observatie geheim. We vertelden de artsen dat we het gebruik van het elektronisch voorschrijfsysteem wilden bestuderen om inzicht te verkrijgen in mogelijkheden tot verbetering. Geneesmiddelvoorschriften in het ziekenhuis zijn doorgaans opdrachten aan de verpleging om medicatie aan de patiënt toe te dienen en worden daarom medicatieopdrachten genoemd. We waren 5 weken lang gedurende kantooruren op de afdeling interne geneeskunde aanwezig en observeerden de invoer van 515 medicatieopdrachten. Bij 34% van deze opdrachten werd een medicatiebewakingsignaal gegenereerd en 91% van alle signalen werd doorgeënterd. 56% van de signalen betrof interacties en deze werden met 98% vaker doorgeënterd dan signalen voor overdosering (89%) of dubbelmedicatie (80%).

Daarnaast analyseerden we de signaalbestanden met alle doorgeënterde signalen over een periode van 2 jaar. Ook bestudeerden we het aantal medicatieopdrachten in die periode. Bij 20% van de opdrachten was er sprake van een doorgeënterd medicatiebewakingsignaal. Binnen deze groep doorgeënterde signalen kwamen interacties het meest voor (59%). Bij nadere beschouwing van de doorgeënterde interacties bleek dat in 36% van de gevallen de effecten van de geneesmiddelcombinatie gecontroleerd zouden kunnen worden met een bepaling in bloed. Voorts bleek dat 76% van de doorgeënterde interacties toe te schrijven was aan slechts twintig interacties.

Dit onderzoek naar doorentergedrag in de dagelijkse praktijk toonde aan dat interacties het vaakst worden doorgeënterd en dat het slechts een klein aantal verschillende interacties betreft. Verder onderzoek naar verbetering van medicatiebewaking zou zich moeten richten op deze frequent doorgeënterde interacties.

De hierboven genoemde studie gaf inzicht in het aantal en type doorgeënterde signalen, maar beantwoordde niet onze vragen waarom signalen worden doorgeënterd, welke cognitieve

processen daarbij een rol spelen en welke fouten worden gemaakt. Dat is het onderwerp van **hoofdstuk 2.3**.

We konden 12 artsen in opleiding tot internist en 6 artsen in opleiding tot chirurg bereid vinden om in een individuele sessie mee te doen met deze simulatiestudie. We vertelden hen dat we de gebruiksvriendelijkheid van Medicator wilden onderzoeken middels een studie die zou lijken op de werksituatie op de afdeling. Het werkelijke doel van de studie, de bestudering van signaalafhandeling, deelden we hen niet mee. We ontwierpen een laboratoriumstudie met casuïstiek van 6 patiënten, met 36 geneesmiddelvoorschriften en 13 verschillende bekende en onbekende medicatiebewakingsignalen. Eerst vertelden we wat de patiënten mankeerden zoals dat ook gebeurt bij de patiëntenoverdracht als de dienst wordt overgenomen. Daarna vroegen we de artsen om voor deze patiënten de medicatieopdrachten in te voeren in een rumoerige omgeving en onder tijdsdruk (zoals dat ook vaak het geval is op de verpleegafdeling). Tijdens de invoer werd de afhandeling van de medicatiebewakingsignalen genoteerd op een observatieformulier. Direct na het beëindigen van de test werd de arts aan de hand van dit formulier ondervraagd waarom hij de signalen zo had afgehandeld.

Dertig procent van de signalen werd onjuist afgehandeld: òf de afhandeling zelf (24%), en/of de reden die achteraf werd genoemd (16%) was fout. De artsen gebruikten in 63% van die foute afhandelingen regels van het type 'als-dan' (als ik dit signaal krijg, dan doe ik dat). Artsen in opleiding tot chirurg gaven twee keer zo vaak een onjuiste reden aan voor hun handelen als artsen die in opleiding waren tot internist. In 13% van de gevallen was de handeling van doorenteren of annuleren wel juist maar werden voor het verklaren van die handeling onjuiste regels gebruikt of regels die niet toegepast mochten worden in de betreffende situatie (bij interne geneeskunde was dit in 5% het geval). Ze gaven bijvoorbeeld aan dat ze de patiënt(parameters) goed zouden controleren, maar noemden dan de verkeerde parameters. Ze zeiden dat ze de concentratie van het geneesmiddel in het bloed zouden controleren, terwijl de geneesmiddelcombinatie geen invloed had op de concentratie in het bloed, maar wèl zou kunnen leiden tot hartritmestoornissen die met een hartfilmpje (elektrocardiogram, ECG) aan het licht zouden kunnen komen. Of ze meldden dat het controleren van de hoeveelheid kalium in het bloed en de nierfunctie voldoende was, terwijl de geneesmiddelcombinatie tot een enorme bloeddrukdaling zou leiden. In sommige buitenlandse elektronische voorschrijfsystemen kan de arts kiezen uit verschillende van tevoren gedefinieerde redenen om medicatiebewakingsignalen door te enteren. Wij denken dat de standaardreden 'patiënt wordt gecontroleerd' onvoldoende is om bovenstaande fouten aan het licht te brengen en te voorkomen.

Verkeerde interpretatie van signalen kwam veel voor en we denken dat ondubbelzinnige, beknopte en duidelijke signaalteksten van groot belang zijn om dit te voorkomen. Eén medicatieopdracht in de test leidde tot twee interacties die in één pop-up scherm werden getoond. Verschillende artsen hadden het tweede signaal onbewust doorgeënterd, mogelijk doordat ze het over het hoofd zagen en dachten dat het doorenteren van de (eerste) interactie nog niet

was gelukt. Studies zijn nodig om te onderzoeken hoe dergelijke dubbele signalen het beste kunnen worden getoond om dit onbewuste doorenteren te voorkomen.

Ongeveer een kwart van de artsen die meededen aan dit onderzoek vertoonden kenmerken van signaalmoeheid, voornamelijk door interacties met lage specificiteit (signalen die niet waren toegesneden op de patiënt). Ze voelden zich overstelpt door de grote aantallen signalen en gaven toe dat ze deze gewoon wegklikten. We denken dat het verhogen van de specificiteit daarom een belangrijke verbetermaatregel is.

Het onderwerp van **hoofdstuk 2.4** is de kwaliteit van de medicatiebewaking in verschillende elektronische voorschrijfsystemen die in Nederlandse ziekenhuizen worden gebruikt. Als maat voor de kwaliteit gebruikten we de sensitiviteit (wordt in een gevaarlijke situatie een signaal gegenereerd) en de specificiteit (is het signaal van toepassing op de patiënt en dus terecht). Of een signaal daadwerkelijk wordt gegenereerd, is afhankelijk van de kennisbank die wordt gebruikt en de functionaliteit van het elektronisch voorschrijfsysteem. Met functionaliteit wordt bedoeld dat het systeem in staat is de aanwezige informatie uit de kennisbank te gebruiken om het signaal te genereren of te onderdrukken. In Nederland hebben we de unieke situatie dat alle elektronische voorschrijfsystemen gebruik maken van dezelfde geneesmiddelenkennisbank, de G-standaard, die veiligheidsinformatie bevat voor alle geregistreerde geneesmiddelen.

We ontwierpen een test, gebaseerd op deze G-standaard, met 29 testonderdelen voor het meten van sensitiviteit en 19 voor specificiteit. In de sensitiviteitstest namen we gevaarlijke situaties op waarin signalen gegenereerd moesten worden. In de specificiteitstest stopten we casuïstiek waarbij signalen niet van toepassing waren op de patiënt en dus niet moesten worden getoond. Als een signaal werd gegenereerd in de sensitiviteitstest was dit dus terecht en in de specificiteitstest was dit onterecht.

We voerden de test uit op 6 verschillende elektronische voorschrijfsystemen die in Nederlandse ziekenhuizen worden gebruikt. 98% van de Nederlandse ziekenhuizen met een elektronisch voorschrijfsysteem werkt met één van deze 6 systemen. In ziekenhuizen kunnen doseergrenzen worden aangepast of interactiesignalen worden uitgezet. Dergelijke lokale aanpassingen zouden bij onze test kunnen leiden tot een vertekend beeld van de medicatiebewakingsfunctionaliteit. Omdat zulke aanpassingen doorgaans niet door de softwareleverancier worden gedaan, voerden we de test uit op het kantoor van de leverancier van het elektronisch voorschrijfsysteem.

Ondanks de gemeenschappelijke kennisbank waarvan alle elektronische voorschrijfsystemen gebruik maken, kwam er uit onze test een enorme variatie in de kwaliteit van de medicatiebewaking. De sensitiviteit varieerde tussen de 0.38 en 0.79 (dat wil zeggen 38% tot 79% van de testonderdelen leidde tot een signaal) en de specificiteit van 0.11 tot 0.84 (in 11% tot 84% van de gevallen was het signaal terecht afwezig). De test bleek dus een goed instrument om verschillen in kwaliteit van de medicatiebewaking te onderscheiden. We hadden gedacht dat systemen met een hoge sensitiviteit een lage specificiteit zouden hebben en andersom.

Het tegendeel bleek waar: in systemen met een hoge sensitiviteit werden onterechte signalen goed onderdrukt en in systemen waarin gevaarlijke situaties regelmatig niet werden gesignaleerd, waren de signalen die wèl werden gegenereerd vaak niet specifiek. Het lijkt erop dat de softwareleveranciers van de beste systemen nieuwe functionaliteit inbouwden zodra deze beschikbaar kwam in de G-standaard, terwijl anderen eerst afwachtten of zorgverleners hiertoe een verzoek indienden.

We onderzochten ook of voor de signalering 1) alleen gegevens uit de medicatieopdracht benodigd waren, of 2) ook gebruik gemaakt werd van patiëntparameters zoals leeftijd, geslacht of gewicht of van 3) laboratoriumgegevens. In de meeste elektronische voorschrijfsystemen was signalering uit de eerste twee categorieën aanwezig en ontbrak de laatste.

Voor de interpretatie van de testresultaten interviewden we 16 ziekenhuisapothekers. Zij kregen de testresultaten van het elektronisch voorschrijfsysteem dat in hun ziekenhuis werd gebruikt op schrift. We vroegen hen of functionaliteit die miste in 'hun' systeem belangrijk was voor de patiëntveiligheid en wat voor extra maatregelen ze hadden getroffen om te voorkómen dat de missende functionaliteit tot medicatiefouten zou leiden. Er waren twee zaken die alle ziekenhuisapothekers belangrijk vonden en die toch ontbraken in 2 van de 6 systemen. Het betrof de bewaking op contra-indicaties en op meerdagenritmes. Een contra-indicatie is een kenmerk van de patiënt waarbij bepaalde geneesmiddelen niet voorgeschreven mogen worden, bijvoorbeeld zwangerschap, epilepsie of penicilline-allergie. Bij ontbrekende functionaliteit voor bewaking op contra-indicaties, kunnen gevaarlijke situaties ontstaan doordat de arts niet wordt geattendeerd op de ongewenste geneesmiddelen. Er is sprake van een meerdagenritme als een geneesmiddel maar eens per 3 dagen of eens per week moet worden ingenomen of toegediend. Als zo'n geneesmiddel eens per dag wordt voorgeschreven, kunnen de gevolgen groot zijn, zeker bij het geneesmiddel methotrexaat.

Over het belang van andere ontbrekende functionaliteit verschilden de meningen van de ziekenhuisapothekers. Ze noemden ook veel verschillende maatregelen om het probleem van ontbrekende functionaliteit tegen te gaan. Deze varieerden van handmatige controle tot klinische beslisregels via de computer.

Het elektronisch voorschrijfsysteem Medicatie/EVS® dat in het Erasmus MC wordt gebruikt had een lage specificiteit van 21% en dit verklaart de waargenomen signaalmoeheid bij artsen. Het feit dat het beste elektronische voorschrijfsysteem een specificiteit van 84% had, suggereert echter dat verbetering mogelijk is.

Vermindering van de last van grote aantallen medicatiebewakingsignalen

In hoofdstuk 3 van dit proefschrift beschrijven we maatregelen die ten doel hebben de last van grote aantallen medicatiebewakingsignalen te verminderen, zonder negatieve effecten op de patiëntveiligheid. We beperken ons in dit hoofdstuk tot de interacties.

Een groep van Nederlandse deskundigen heeft ten behoeve van de Nederlandse geneesmiddelenkennisbank, de G-standaard, alle geneesmiddelcombinaties die in de literatuur worden

aangemerkt als interactie gecategoriseerd op basis van optredend effect (ja of nee), de mogelijkheid om actie te ondernemen (ja of nee), de mate van bewijs (van 0 tot 4) en de ernst van de gevolgen (van A tot F). In de G-standaard zijn interacties ingedeeld als ja/ja (een interactie die actie behoeft), ja/nee (een interactie die geen actie behoeft), nee/nee (een combinatie die in de literatuur wordt aangemerkt als interactie maar dat eigenlijk niet is en ook geen actie behoeft). De interacties hebben een alfanumerieke code die aangeeft wat de ernst en bewijslast van de interactie is. De G-standaard omvat ook standaardteksten voor de medicatiebewakingsignalen. Met deze nationale geneesmiddelenkennisbank ontwikkeld door en voor apothekers is Nederland in het voordeel ten opzichte van andere landen die met verschillende commerciële kennisbanken werken zonder transparante en eenduidige categorisering op basis van ernst, bewijslast en te ondernemen actie.

In het Erasmus MC is het elektronisch voorschrijfsysteem Medicatie/EVS® zo ingesteld dat alleen interacties van de categorie ja/ja leiden tot een interactiesignaal. Het systeem toont de door de G-standaard gemaakte signaalteksten. De alfanumerieke code die iets zegt over ernst en bewijslast van de interactie is niet zichtbaar voor de arts.

We hebben eerst maatregelen bestudeerd die gericht waren op het verbeteren van de werkbaarheid voor de arts. In **hoofdstuk 3.1** beschrijven we een studie die tot doel had de overmatige signalering op een veilige manier te verminderen. We dachten dat sommige signalen in het ziekenhuis veelvuldig werden doorgeënterd en veilig uitgezet zouden kunnen worden vanwege de (mogelijkheden voor) intensieve controle van patiënten (zoals bloeddrukmetingen, ECG's en bepalingen in bloed). We selecteerden signalen die vaker dan 10 keer in één maand werden doorgeënterd. Interacties die geen alfanumerieke code hadden, namen we niet mee omdat we dachten dat de ernst van de interactie een belangrijke rol zou spelen bij de beslissing over het al dan niet uitzetten van het signaal. Ook signalen met betrekking tot de toediening van geneesmiddelen namen we niet mee omdat we dachten dat deze het best door de verpleging afgehandeld zouden kunnen worden (zie hoofdstuk 3.3). We maakten schermafdrukken van de interactiesignalen en vroegen aan 18 artsen van interne geneeskunde, cardiologie en chirurgie en aan 6 ziekenhuisapothekers of deze signalen veilig uitgezet zouden kunnen worden voor het hele ziekenhuis. Ook vroegen we hen naar de redenen daarvoor. De tekst van de signalen is vaak langer dan wat er in eerste instantie op het pop-up scherm zichtbaar is. Daarom stelden we dezelfde vraag nogmaals met de volledige geprinte signaaltekst (die normaal alleen te lezen is als de arts in de tekst naar beneden scrollt).

Het merendeel van de respondenten vond dat signalen uitgezet moesten worden, alhoewel alleen ja/ja-interacties (die actie behoeven) waren meegenomen in deze test. Er was echter geen enkel interactiesignaal waarover iedereen het eens was dat deze voor het hele ziekenhuis veilig kon worden uitgezet. De hoogste mate van overeenstemming was 13 van de 24 respondenten (54%). Een kwart van de respondenten vond dat signalen helemaal niet ziekenhuisbreed moesten worden uitgezet. De signalen stoorden hen helemaal niet (wat suggereert dat

de ervaren overlast van overmatige signalering individueel afhankelijk is) of ze vreesden dat het uitzetten zou leiden tot het maken van fouten door arts-assistenten en chirurgen (terwijl de signalen deze fouten zouden kunnen voorkomen). Ook bleek dat bepalingen in bloed die in de signaalteksten worden geadviseerd al routinematig werden verricht voor patiënten op de afdelingen interne geneeskunde en cardiologie maar dat dit op de afdeling chirurgie geen routine was. Het ziekenhuisbreed uitzetten van dergelijke signalen bleek dus problematisch.

Er was niet alleen gebrek aan overeenstemming over het al dan niet uitzetten van de verschillende signalen, per signaal bleek er ook verschil van mening te bestaan over de redenen daarvoor. Dit verschil van mening bestond zowel tussen de verschillende specialismen als ook tussen de verschillende respondenten binnen één specialisme. Veelvuldig genoemde redenen om signalen uit te zetten waren: het effect van de combinatie is bekend, is niet ernstig, wordt gecontroleerd of beoogd òf de interactie behoeft geen actie.

Verscheidene redenen voor uitzetten die werden genoemd waren vanuit veiligheidsoogpunt voor discussie vatbaar. Als het effect van de combinatie wordt beoogd door sommige specialisten, dan hoeft dit niet voor (alle) artsen van andere specialismen te gelden. Als iets alleen door specialisten zou (moeten) worden voorgeschreven, wil dit niet zeggen dat het nooit per ongeluk door een arts wordt gedaan zonder ervaring met het middel of de combinatie. De mening dat geen actie benodigd is, wordt niet gedeeld door de groep van experts die de literatuur heeft bestudeerd en de betreffende interactie als ja/ja heeft gecategoriseerd. De respondenten die meldden dat een interactie uitgezet zou kunnen worden omdat deze bekend is, hebben geen rekening gehouden met het feit dat fouten vaak worden gemaakt door vergeetachtigheid, verminderde aandacht of als men afgeleid wordt, en veel minder vaak door een gebrek aan kennis.

Opvallend was dat de respondenten het aantal keren dat een signaal wordt getoond of doorgeënterd vrijwel niet noemden. Toch was er een positieve correlatie tussen het aantal keer dat een signaal was doorgeënterd en het aantal dokters dat het signaal wilde uitzetten: hoe vaker doorgeënterd, hoe vaker het verzoek om het signaal uit te zetten. Veel respondenten gaven spontaan negatief commentaar op de lengte, de inhoud of de volgorde van de landelijke signaalteksten, alhoewel het niet het doel van de studie was om dát te onderzoeken.

De resultaten van deze studie suggereren dat het al dan niet tonen van interactiesignalen niet ziekenhuisbreed moet worden ingesteld, maar gebaseerd moet zijn op het specialisme of op het kennisniveau van de arts. Hierbij lijkt het zinvol de signalen die men zou willen uitzetten op een meer subtiele manier te tonen zonder het werkproces te onderbreken, bijvoorbeeld door een icoontje dat men op een geschikt moment kan aanklikken om de inhoud te bekijken. Het aanpassen van de signaalteksten (korter, duidelijker) zou mogelijk de benodigde energie voor het afhandelen van de signalen kunnen verminderen en daarmee tevens de signaalmoeheid kunnen tegengaan.

In **hoofdstuk 3.2** beschrijven we een dergelijke aanpassing in de signaaltekst. We voegden boven aan de signaaltekst in hoofdletters één regel toe met een beschrijving van de ernst van de interactie en met de alfanumerieke code die iets zegt over ernst en bewijslast. We hanteerden 3 categorieën: lage, middelmatige en hoge ernst. We bestudeerden voor en na deze aanpassing of het aantal doorgeënterde interacties in totaal en per ernstcategorie veranderde. We relateerden deze aantallen aan het aantal voorgeschreven medicatieopdrachten in dezelfde periode. Ook vroegen we een aantal artsen of deze extra regel hen hielp bij de afhandeling van de interacties.

Het aantal doorgeënterde signalen per medicatieopdracht nam statistisch significant toe van 10.8% tot 12.8% (18% toename, $p < 0.001$). We zagen deze toename bij alle ernstcategorieën. De toename was het hoogst voor signalen met middelmatige ernst (24.8%) en lager voor signalen met lage (12.3%) en hoge ernst (6.2%).

We vroegen 69 artsen die een interactiesignaal hadden doorgeënterd of ze de toegevoegde regel met de ernstvermelding hadden opgemerkt en handig vonden. Tweeënveertig artsen beantwoordden onze vragen en 62% daarvan gaf aan dat de informatie hen hielp bij de signaalafhandeling, alhoewel ze de alfanumerieke code daarvoor niet gebruikten.

Het toegenomen aantal doorgeënterde signalen per medicatieopdracht hoeft niet te betekenen dat signalen na de aanpassing meer genegeerd werden door signaalmoeheid. Het zou ook zo kunnen zijn dat artsen patiënten meer zijn gaan controleren, maar dat hebben we niet onderzocht. Aangezien het merendeel van de respondenten aangaf dat de extra informatie hielp bij de signaalafhandeling, concludeerden we dat deze toevoeging de signaalmoeheid helpt verminderen.

In de laatste delen van hoofdstuk 3 beschrijven we het risico voor de patiënt in gevallen waarbij de arts interactiesignalen heeft doorgeënterd. We hebben 2 verschillende groepen veelvuldig doorgeënterde interacties met een lage specificiteit onder de loep genomen: tijdsinteracties en QT-interacties. In **hoofdstuk 3.3** beschrijven we de tijdsinteracties. Dit zijn combinaties van geneesmiddelen die bij gelijktijdige inname een verminderd effect hebben en bij inname met een tijdsinterval van bijvoorbeeld 2-4 uur elkaars werking niet negatief beïnvloeden. Het bijbehorende interactiesignaal geeft aan welk minimaal tijdsinterval benodigd is. Als de geneesmiddelen toch gelijktijdig of te snel na elkaar worden toegediend of ingenomen, is er sprake van een medicatiefout, die we in dit geval toedienfout noemen. Het doel van ons onderzoek was om bij deze tijdsinteracties het aantal toedienfouten te verminderen. We hebben aan de hand van de doorgeënterde tijdsinteracties onderzocht of de arts in het voorschrijfsysteem de toedientijd had aangepast naar het juiste tijdsinterval. Ook hebben we op de verpleegafdeling gekeken of de tijden op de toedienlijst voor de verpleging overeenstemden met het benodigde tijdsinterval.

In eerste instantie werd voor meer dan de helft van de patiënten met een tijdsinteractie niet het benodigde tijdsinterval in acht genomen (56.4%). Na een les voor artsen en verpleegkundigen,

het uitdelen van een tabel met de juiste tijdsintervallen en dagelijkse terugkoppeling van de foutieve toedienmomenten daalde dit naar 36.2%. Dit was voornamelijk toe te schrijven aan verpleegkundigen die zelf de toedientijden aanpasten, terwijl de artsen het slechts in 21% van de gevallen juist voorschreven. Twee jaar later deden we een soortgelijke studie op 28 (in plaats van 8) afdelingen en vonden we 46.7% toedienfouten. We stelden voor dat verpleegkundigen in plaats van artsen de tijdsinteractiesignalen zouden afhandelen. Toen dit op bezwaren stuitte, vroegen we apothekersassistenten naar de afdeling te gaan om tijdsintervallen te controleren en indien nodig te vragen om aanpassing van toedientijden. Het aantal toedienfouten (45.2%) en voorschrijffouten (81%) van deze geneesmiddelcombinaties bleef hoog.

Om te begrijpen waarom het aantal toedienfouten niet drastisch verminderd kon worden, namen wij het proces van signaalafhandeling van tijdsinteracties verder onder de loep. Dit proces bleek inefficiënt en foutgevoelig. De medicatieopdracht moest worden geannuleerd en dan opnieuw voorgeschreven, òf moest eerst worden vastgelegd voordat wijziging van toedientijden kon plaatsvinden. Een knop voor aanpassing van (de toedientijden in) de medicatieopdracht ontbrak maar verdient natuurlijk de voorkeur. Als de arts vervolgens de geneesmiddelen met het juiste tijdsinterval had voorgeschreven, kreeg hij weer hetzelfde tijdsinteractiesignaal te zien. Dit komt doordat voor de signalering uitsluitend gebruik wordt gemaakt van de geneesmiddelen en niet van de ingevoerde tijden, wat leidt tot een lage specificiteit. Het belangrijkste deel van de signaaltekst (met het benodigde tijdsinterval) valt net buiten het pop-up scherm en kan alleen worden gelezen als naar beneden wordt gescrolld. Het systeem maakt het de artsen dus wel erg moeilijk om deze interactiesignalen juist af te handelen. Om een juiste afhandeling te bewerkstellingen zou de G-standaard de signaalteksten moeten aanpassen en het benodigde tijdsinterval gecodeerd moeten opnemen. De elektronische voorschrijfsystemen zouden deze gecodeerde tijdsindicaties moeten gebruiken om het signaal te onderdrukken bij een juist tijdsinterval en bij een onjuist tijdsinterval efficiënte aanpassing middels een 'aanpasknop' moeten ondersteunen.

QT-interacties worden ook veelvuldig doorgeënterd. QT-interactiesignalen waarschuwen voor verlenging van een bepaald onderdeel van het ECG, het QT-interval. Verlenging van dit QT-interval verhoogt de kans op Torsades de Pointes, een hartritmestoornis die kan leiden tot plotse dood. Een patiënt met een QT-interval van meer dan 500 milliseconden (msec), of een toename van meer dan 60 msec, wordt beschouwd als risicopatiënt voor het ontwikkelen van Torsades de Pointes. Risicofactoren voor QT-verlenging zijn onder meer hoge leeftijd, vrouwelijk geslacht, hart- en vaatziekten, langzame hartslag en lage kaliumconcentratie in het bloed. Verschillende geneesmiddelen kunnen ook in meerdere of mindere mate QT-verlenging geven en de dosis van het geneesmiddel en de mate van uitscheiding door de nier spelen daarbij ook een rol. Bij een combinatie van twee of meer QT-verlengende geneesmiddelen is een ECG gewenst om het QT-interval en de kans op Torsades de Pointes te bepalen.

In **hoofdstuk 3.4** laten we zien hoe vaak ook daadwerkelijk een ECG wordt gemaakt als een QT-interactiesignaal wordt doorgeënterd en hoe vaak er dan sprake is van een verlenging van het QT-interval met kans op Torsades de Pointes. Uit alle doorgeënterde QT-interactiesignalen in een periode van 6 maanden selecteerden we de opgenomen patiënten zonder pacemaker (want die kan de QT-verlenging voorkómen). Ook namen we de patiënten die de combinatie van co-trimoxazol en tacrolimus gebruikten niet mee, omdat we dit als een geneesmiddelcombinatie met een laag risico beschouwden. We selecteerden 168 patiënten en zochten uit of ze risicofactoren hadden voor QT-verlenging, welke QT-verlengende geneesmiddelen ze hadden gebruikt en of een ECG beschikbaar was. Slechts voor 33% van de patiënten was er een ECG gemaakt binnen een maand na het starten van de combinatie van QT-verlengende geneesmiddelen. We hadden een hoger percentage verwacht omdat zonder ECG de kans op deze ernstige hartritmestoornissen niet kan worden bepaald. Patiënten met een ECG hadden meer risicofactoren voor QT-verlenging en een hoger aantal doorgeënterde QT-interacties dan patiënten waarvoor geen ECG was gemaakt. Wij konden uit de gegevens niet opmaken of die ECG's nu waren gemaakt vanwege de hart- en vaatziekten van de patiënt òf ten gevolge van het verschenen QT-interactiesignaal. Dit zou kunnen betekenen dat zelfs in minder dan 33% van de gevallen het QT-interactiesignaal leidt tot het maken van een ECG.

Bij beschouwing van het proces van signaalafhandeling kwamen we weer dezelfde problemen tegen als beschreven in hoofdstuk 3.3: zowel de signaaltekst, de afhandeling, als de lage specificiteit bleken fouten uit te lokken. Het advies om een ECG te maken staat niet bovenaan in de signaaltekst en kan alleen worden gelezen door de tekst naar beneden te scrollen. Als de arts een ECG wil aanvragen, dan kan dat niet in het elektronisch voorschrijfsysteem. De specificiteit van het signaal wordt bepaald door de relevantie (ernst), urgentie (de noodzaak direct actie te ondernemen) en de mate waarin het signaal is toegesneden op de patiënt. De QT-interactiesignalen zijn zeker relevant, aangezien de combinatie kan leiden tot ernstige hartritmestoornissen. De signalen zijn ook urgent omdat eigenlijk al voor starten van de combinatie een ECG moet worden gemaakt om de toename in het QT-interval te kunnen beoordelen. De QT-signalen zijn echter niet toegesneden op de patiënt omdat de signalering geen gebruik maakt van de leeftijd, het geslacht, de kaliumconcentratie in het bloed, de nierfunctie en eventuele andere ziekten van de patiënt. De specificiteit kan alleen worden verhoogd door een koppeling tussen elektronisch voorschrijfsysteem en laboratorium- (en andere) gegevens van de patiënt.

Bij 29% van de patiënten was er zowel voor als na het starten van de QT-verlengende geneesmiddelcombinatie een ECG beschikbaar. Bij 31% van deze patiënten was er daadwerkelijk sprake van een verhoogd risico op Torsades de Pointes, vergeleken met een controlegroep die één QT-verlengend geneesmiddel gebruikte.

Het feit dat slechts voor weinig patiënten ECG's werden gemaakt en het grote percentage patiënten met een verhoogd risico op Torsades de Pointes binnen de groep met twee ECG's, suggereert dat patiënten risico lopen als ze een combinatie van twee QT-verlengende geneesmiddelen krijgen voorgeschreven. Artsen die deze combinaties voorschrijven zouden beter

geïnformeerd moeten worden over de noodzaak van het maken van een ECG. Dit kan door duidelijker signaalteksten, maar ook door apothekers die contact zoeken met de arts als ECG's toch niet zijn gemaakt.

In hoofdstuk 3.4 bespraken we de lage specificiteit van QT-interactiesignalen. In 2006 werd in het Pharmaceutisch Weekblad door ziekenhuisapothekers aangegeven dat slechts bij een beperkt aantal geneesmiddelen actie nodig was. Vervolgens ontstond een discussie over klinische relevantie van de signalen, risico-inschatting en over de werkwijze van de commissie die gestructureerd bepaalt welke interacties in de G-standaard worden opgenomen. In het voorjaar van 2007 werd de G-standaard op dit punt aangepast: het aantal geneesmiddelen dat kan leiden tot deze interactie werd beperkt zodat minder onterechte signalen zouden worden gegenereerd (hogere specificiteit).

In **hoofdstuk 3.5** beschrijven we ons onderzoek naar deze aanpassing. Wij onderzochten of de aanpassing inderdaad zou leiden tot minder signalen, of de signalen vaker terecht zouden zijn en of de risicopatiënten minstens even goed zouden worden geïdentificeerd. We gebruikten de 49 patiënten uit hoofdstuk 3.4 waarbij ECG's voor en na de (oude) QT-interactie waren gemaakt. We bekeken of met de aangepaste G-standaard ook een signaal zou worden gegenereerd en we beoordeelden het risico op Torsades de Pointes. Het aantal signalen zou met de aangepaste G-standaard afnemen met 53%. De positief voorspellende waarde van de QT-signalen die iets zegt over de kans dat een patiënt met een QT-signaal inderdaad risico loopt (specificiteit) steeg echter niet, maar bleef gelijk. Bovendien bleek dat met de aangepaste signalering 53% van de risicopatiënten niet zou worden geïdentificeerd. Deze aangepaste signalering leidde dus tot een slechtere indentificatie van risicopatiënten en daarom besloten we om deze niet te implementeren in het Erasmus MC.

Deze onbedoelde effecten werden veroorzaakt doordat alleen de geneesmiddelklasse werd meegenomen in de QT-signalering en de vele andere risicofactoren voor QT-verlenging (zoals hoge leeftijd, vrouwelijk geslacht, lage kaliumconcentratie in het bloed) niet. Het is eerst noodzakelijk om de bijdrage van de afzonderlijke risicofactoren aan QT-verlenging in kaart te brengen voordat een klinische beslisregel kan worden gemaakt die wel is toegesneden op de patiënt.

Conclusies

Het model van Reason helpt om te begrijpen hoe verschillende aspecten van medicatiebewaking in elektronische voorschrijfsystemen fouten door artsen kunnen uitlokken, zoals het negeren, verkeerd interpreteren of verkeerd afhandelen van signalen.

Signaalmoeheid is moeheid die leidt tot het onterecht doorenteren van relevante waarschuwingssignalen omdat het beoordelen en afhandelen van deze signalen teveel tijd en mentale energie kosten. Signaalmoeheid wordt veroorzaakt door signalen met lage specificiteit, ondui-

delijke signaalteksten, signalen die onnodig het werkproces onderbreken en/of die waarbij de afhandeling inefficiënt is.

Er is veel ruimte voor verbetering, alhoewel het moeilijk is om signaalmoeheid tegen te gaan. Er zijn aanpassingen nodig in de Nederlandse geneesmiddelendatabank (G-standaard), het elektronisch voorschrijfsysteem, als ook in het ziekenhuis zelf. Het elektronisch voorschrijfsysteem en de daarin opgenomen medicatiebewaking kan niet los worden gezien van het ziekenhuis waarin het wordt gebruikt. Artsen, specialismen en ziekenhuizen verschillen in geneesmiddelkennis, vastgelegde en veronderstelde verantwoordelijkheden en in het aantal bepalingen in bloed dat routinematig (zonder een getoond medicatiebewakingsignaal) plaatsvindt. Het is daarom noodzakelijk dat wijzigingen in de medicatiebewaking met de nodige voorzorgen, controlemomenten en uitkomstmetingen worden geïntroduceerd.

EPILOOG

Iemand die hoofdpijn heeft, die geef je een tabletje,
iemand die koortsig is, die stuur je naar z'n bedje,
iemand die keelpijn heeft, die laat je gauw behandelen,
dan zegt de dokter: 't zijn waarschijnlijk de amandelen.
Maar iemand die humeurig is, die laten ze maar lopen,
omdat de apothekers daar geen pillen voor verkopen.

Als je verkouden bent dan slik je aspirines,
en ben je lusteloos dan neem je vitamines,
honderden middeltjes voor allerhande kwalen
die je bij alle apothekers kunt gaan halen,
maar iemand die humeurig is die laten ze maar lopen,
omdat je daar nog steeds geen doosje pillen voor kunt kopen.

Bovenstaand gedicht van Annie M.G. Schmidt suggereert dat apothekers van dienst kunnen zijn bij allerlei medische problemen, maar geen oplossing hebben voor mensen die humeurig zijn.

Als ziekenhuisapotheker verantwoordelijk voor de implementatie van het elektronisch voorschrijfsysteem binnen het Erasmus MC kreeg ik regelmatig opmerkingen van humeurige artsen over de veelheid aan onnodige signalen die ze zonder te lezen wegklikten. Ik heb me die opmerkingen aangetrokken en ik heb gezocht naar oplossingen. Daarbij heb ik medewerking gekregen van veel artsen die zich lieten observeren of interviewen.

Het resultaat is geen doosje pillen maar een proefschrift met inzichten over signaalmoeheid door medicatiebewaking in elektronische voorschrijfsystemen. Ik hoop dat het systeem met deze inzichten beter werkbaar èn veiliger wordt.

Ik wil alle artsen van het Erasmus MC bedanken voor hun kritiek en hun medewerking. Zonder jullie was dit proefschrift er niet gekomen en daarom draag ik het graag aan jullie op.

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Heleen

LIST OF PUBLICATIONS

Publications related to this thesis

Van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006;13(2):138-47.

Van der Sijs H, Mulder A, Van Gelder T, Aarts, J, Berg M, Vulto A. Drug safety alert generation and overriding in a large Dutch university medical centre. Pharmacoepidemiol Drug Saf 2009 (In press).

Van der Sijs H, Van Gelder T, Aarts J, Vulto A, Berg M. Understanding handling of drug safety alerts: a simulation study. Submitted.

Van der Sijs H, Bouamar R, Van Gelder T, Aarts J, Berg M, Vulto A. Functionality test for drug safety alerting in computerized physician order entry systems. Submitted.

Van der Sijs H, Aarts J, Van Gelder T, Berg M, Vulto A. Turning off frequently overridden drug alerts: limited opportunities for doing it safely. J Am Med Inform Assoc 2008;15(4):439-48.

Van der Sijs H, Mulder A, Van Gelder T, Aarts J, Berg M, Vulto A. Addition of level of seriousness to drug safety alert texts: better informed but increased overriding. Submitted.

Van der Sijs H, Lammers L, Van den Tweel A, Aarts J, Berg M, Vulto A, Van Gelder T. Time-dependent drug-drug interaction alerts in computerized physician order entry: software hampers drug administration error reduction. Submitted.

Van der Sijs H, Kowlesar R, Klootwijk APJ, Nelwan SP, Vulto AG, Van Gelder T. Clinically relevant QTc-prolongation due to overridden drug-drug interaction alerts: a retrospective cohort study. Br J Clin Pharmacol 2009;67(3):347-54.

Van der Sijs H, Kowlesar R, Aarts J, Berg M, Vulto A, Van Gelder T. Unintended consequences of reducing QT-alert overload in a computerized physician order entry system. Eur J Clin Pharmacol 2009 May 5 (Epub ahead of print).

Other publications related to CPOE

In English

Van den Tweel AMA, *Van der Sijs IH,* Van Gelder T, Knoester PD, Vulto AG. Computerized medication alert signals: does the MD no longer need the PharmD? Eur J Hosp Pharm 2006;12(2):30-2.

Van der Sijs H. Computerised drug alerts: progress, but a long way to go. Hospital pharmacy Europe 2007;(33):56-7.

Pirnejad H, Niazkhani Z, *Van der Sijs H,* Berg M, Bal R. Impact of a computerized physician order entry system on nurse-physician collaboration in the medication process. Int J Med Inform 2008;77(11):735-44.

Niazkhani Z, *Van der Sijs H,* Pirnejad H, Redekop W, Berg M, Aarts J. Same system, different outcomes: comparing the transitions from two paper-based systems to the same computerized physician order entry system. Int J Med Inform 2009;78 (3):170-81.

Niazkhani Z, Pirnejad H, De Bont A, *Van der Sijs H,* Aarts J. Computerized provider order entry system – Does it support the inter-professional medication process? Methods Inf Med 2009 May 15 (Epub ahead of print).

Pirnejad H, Niazkhani Z, *Van der Sijs H,* Berg M, Bal R. Evaluation of the impact of a CPOE system on nurse-physician communication - a mixed method study. Methods Inf Med 2009 May 15 (Epub ahead of print).

Aarts J, *Van der Sijs H*. CPOE, alerts and workflow: taking stock of ten years research at Erasmus MC. Proceedings Patient Safety through Intelligent Procedures in medication 2009 September 24-25 (In press).

In Dutch

Bartelink IH, *Van der Sijs IH.* Minder fouten door elektronisch voorschrijven in ziekenhuizen. Nieuwe systemen brengen nieuwe risico's. Pharm Weekbl 2003;138(20):713-9.

Van der Sijs IH, Hooghiemstra TFM. Hoe het moet, hoe het mag en hoe het zou kunnen. Juridische aspecten van elektronisch voorschrijven in ziekenhuizen. Pharm Weekbl 2004;139 (38):1224-8.

Van der Sijs IH, Hooghiemstra TFM. Nieuwe vragen. Juridische aspecten van elektronisch voorschrijven in polikliniek en bij ontslag uit het ziekenhuis. Pharm Weekbl 2005;140(37):1158-61.

Van der Sijs IH. Van handgeschreven tot geprint recept: een veranderingsproces met vele kanten. In: Wagner C, Van der Wal G, Tuijn S. Patiëntveiligheid in Nederland. Verbeterinitiatieven en innovaties in de zorg. Assen, Koninklijke van Gorcum, 1e Ed, 2005.

CURRICULUM VITAE

Heleen van der Sijs werd op 11 juni 1967 geboren te Zwollerkerspel (thans Berkum, gemeente Zwolle). In 1985 behaalde zij het VWO-diploma aan het Revius Lyceum te Doorn en begon ze met de studie Farmacie aan de Rijksuniversiteit Utrecht. Tijdens de doctoraalfase behaalde zij haar diploma stralingshygiëne niveau 3 en volgde zij extra colleges ethiek bij de faculteit theologie, uitmondend in een doctoraalscriptie over farmaceutische beroepsethiek. Ze haalde haar propedeuse en doctoraal examen met genoegen. Na een extra stage tropische geneeskunde in Ecuador sloot zij haar studie in 1992 af met het apothekersexamen.

In datzelfde jaar startte zij als projectapotheker in het Academisch Medisch Centrum te Amsterdam, waar zij 8.5 jaar bleef werken. Van 1994 tot 1997 werd zij daar opgeleid tot ziekenhuisapotheker door dr. P.J. Roos. Daarna had zij als ziekenhuisapotheker in het AMC de aandachtsgebieden klinische dienstverlening, kinderfarmacie en radiofarmacie. Vanaf eind 1999 hield zij zich bezig met de implementatie van het elektronisch voorschrijven.

In mei 2001 trad zij als ziekenhuisapotheker in dienst van het Erasmus MC in Rotterdam. Zij was als projectleider verantwoordelijk voor de klinische en poliklinische implementatie van elektronisch voorschrijven op de verschillende locaties van het Erasmus MC. In 2003 volgde zij de Leergang Zorg Informatiemanagement van het Instituut voor Beleid en Management in de Gezondheidszorg en ontstond het idee voor het onderzoek beschreven in dit proefschrift. Sinds 2006 is zij voornamelijk werkzaam in het Sophia Kinderziekenhuis. Heleen is getrouwd met Nico Sizoo. In haar vrije tijd maakt ze graag muziek: ze speelt blokfluit op semi-professioneel niveau en houdt van zingen.

Heleen van der Sijs was born on June 11, 1967 in Zwollerkerspel, the Netherlands. In 1985 she graduated from secondary school at the Revius Lyceum in Doorn and started her pharmacy study at the University of Utrecht. She obtained her Master of Science degree with distinction with a dissertation on pharmaceutical ethics. In 1992 she did a traineeship on tropical diseases in Ecuador and obtained her pharmacist's degree.

In the same year she started as a pharmacist in the hospital pharmacy of the Academic Medical Center in Amsterdam. From 1994 to 1997 she was trained as a hospital pharmacist in the same hospital. After this specialisation she kept working in the AMC as a hospital pharmacist with an interest in pediatric pharmacy and CPOE.

In May 2001, she started working in the Erasmus University Medical Center in Rotterdam. She was a project leader for the CPOE implementation for in- and outpatient clinics of Erasmus MC. In 2003 she did a course on Health Information Management at the Institute of Health Policy and Management, which raised her interest in doing the PhD research described in this thesis. From 2006 on, she is mainly working at the Sophia Children's Hospital of Erasmus MC. Heleen is married to Nico Sizoo. In her spare time she likes to make music, she plays recorder semiprofessionally and loves singing.

PhD PORTFOLIO

Summary of PhD training and teaching activities related to the PhD research

PhD training

Conferences, study tours and courses	Year	Hours
Leergang Zorg Informatie Management (iBMG)	2003	80
Studiereis Medicatieveiligheid en ICT-toepassingen USA (OPG Distrimed)	2003	40
Terugkomdag studiereis medicatieveiligheid en ICT-toepassingen (OPG Distrimed)	2003	6
Medicatieveiligheid (PUOZ)	2003	6
Zorg ICT-congres MIC2003	2003	12
Terugkomdag Leergang Zorg Informatie Management (iBMG)	2004	6
Medicatieveiligheid in het ziekenhuis: analyse, visie en beleid (OPG Distrimed)	2004	6
10th Congress of European Association of Hospital Pharmacists, Lisboa (EAHP)	2005	13
Medicatieveiligheid (PUOZ)	2005	5
40th American Society of Health-System Pharmacists Midyear Clinical Meeting, Las Vegas (ASHP)	2005	20
Bedside pharmacy symposium (Brocacef)	2006	6
2007 International Forum on Quality and Safety in Health Care, Barcelona (BMJ/IHI)	2007	18
Validatie van Software (PUOZ)	2007	6
Patiëntveiligheid: voorkom schade, werk veilig (IGZ)	2007	5
Tweede Nederlandse Ziekenhuisfarmaciedag (NVZA)	2007	6
Nederlandse promovendidagen medische informatica (Renesse)	2008	10
13th Congress of European Association of Hospital Pharmacy, Maastricht (EAHP)	2008	13
Derde Nederlandse Ziekenhuisfarmaciedag (NVZA)	2008	6
14th Congress of European Association of Hospital Pharmacy, Barcelona (EAHP)	2009	13

Presentations on conferences, courses and seminars	Year
Implementeren is laveren (MIC2003, Veldhoven)	2003
Medicator: elektronisch voorschrijven in het Erasmus MC (Leergang Zorg Informatie Management, iBMG, Rotterdam)	2004
Pitfalls van het EVS (PUOZ-cursus Medicatiebegeleiding voor ziekenhuisapothekers in opleiding, Utrecht)	2005
Implementeren is laveren (Minisymposium voorafgaand aan promotie JCEM Aarts, Rotterdam)	2005
Foutenvermindering door elektronisch voorschrijven? (PUOZ-cursus Medicatieveiligheid, Utrecht)	2005
Medicatiecatieveiligheid (Minisymposium Rondom Patiëntveiligheid, Erasmus MC Rotterdam)	2005
CPOE in Erasmus MC (Erasmus International Mastercourse on Health Information Management, iBMG, Rotterdam)	2006
CPOE in Erasmus MC (Erasmus International Mastercourse on Health Information Management, iBMG, Rotterdam)	2007
Functionality of drug safety alerting in Dutch computerized physician order entry systems (EAHP, Maastricht)	2008
Drug safety alerting in computerized physician order entry (Nederlandse promovendidagen medische informatica, Renesse)	2008
Unintended consequences of reducing QT-alert overload (Derde Ziekenhuisfarmaciedag, NVZA, Rotterdam)	2008
Drug safety alerting and the risk of alert fatigue (EAHP, Barcelona)	2009

Posters	*Year*
Implementation of computerized physician order entry: impact on nurse satisfaction. (EAHP, Lisboa)	2005
Effect of level of seriousness presentation on drug-drug interaction overriding in computerized physician order entry. Tweede Nederlandse Ziekenhuisfarmaciedag (NVZA, Leiden)	2007

Teaching

Supervising Masters's theses Zorg Management and Research Projects Pharmacy	Years	Hours
Manon Hendriks. Elektronische satisfactie. (iBMG)	2004	30
Wijnie Nijssen. Wie schrijft er voor? Onderzoek naar de beïnvloeding van het voorschrijfgedrag door een elektronisch voorschrijfprogramma richting apotheekassortiment. (iBMG)	04/05	30
Noortje Meijnen. Elektronisch voorschrijven. Een kwestie van tijd. (iBMG)	04/05	30
Inke van Dam. Medicator op de polikliniek. Wensen van artsen en randvoorwaarden van de apotheek. (iBMG)	04/05	30
Annemieke van den Tweel. Elektronische medicatiebewaking. Is er extra controle nodig vanuit de apotheek? (RUU)	04/05	45
Japke Hartogsveld. Medication safety. Overriding and handling of drug safety alerts in Medicator. (RUU)	2006	45
Rachida Bouamar. Functionality of Dutch Computerized Physician Order Entry Systems. (RUU)	06/07	45
Ravi Kowlesar. Clinically relevant QTc-interval prolongation as a result of combining two drugs that prolong the QTc-interval: a retrospective cohort study. (RUU)	06/07	45
Shantie Anant. Drug safety alerts. (RUU)	06/07	45
Alexandra Mulder. Override rates of drug safety alerts in computerised physician order entry. (RUU)	2007	45
Serpil Huy. Pediatric overdose alerts in Medicatie/EVS®. (RUU)	08/09	45

Other teaching and training	Years	Hours
Lecturing (pharmacy teaching for students in medicine in Erasmus MC)	03/09	200
Pharmacy teaching for nurses in Erasmus MC	03/09	40
Student Editorial Board 'Methods of Information in Medicine'	2009	8
Other symposia and conferences to fulfil continuous education requirements for hospital pharmacy specialisation	03/09	124