Clinical rules in hospital pharmacy practice to prevent adverse drug events

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Voor Mees & Saar

Contents

Part I

Introduction

1

General introduction

Adverse drug events (ADEs) refer to any injury resulting from the use of a drug [1,2]. ADEs can be due to a medication error (intrinsic harm) or an adverse drug reaction (ADR) (extrinsic harm) [3-5]. Worldwide many patients suffer from drug related problems such as ADEs. Indeed, the report "To Err is Human" by the Institute of Medicine shows that a considerable number of people die each year in hospitals partially due to medication related harm [6]. In addition, drugs are the leading cause of adverse events in the Medical Practice Study [7]. Since then, ADEs have been a subject of intense research.

A literature review by Krahenbuhl-Melcher et al. conclude that overall in about 6% of hospitalized patients ADEs occur, with a wide range among the different studies (0.17–65%), and that approximately 50% are considered preventable [8]. The wide range can partly be explained by the different ADE detection methods that are used in studies, such as voluntary report of ADEs, chart review or computer based monitoring systems to detect ADEs [9,10]. ADEs in hospitalized patient do lead to extra costs and prolonged length of stay in the hospital [11-13].

Also in The Netherlands some data is available about the incidents frequency of ADEs. Van der Hooft et al. investigated ADR-related hospitalizations and found that in 2001 1.83% and in 2003 5.1% of acute hospital admissions are ADR related [14,15]. Leendertse et al. shows in their HARM study that of almost 13000 unplanned admissions in the hospital 714 (5.6%) are medication related, and that almost half of these admissions are potentially preventable [16]. More recently, a prospective chart review shows that more than half of the patients admitted to the hospitals are experiencing harm of ADEs, of which most are non-serious, non-preventable ADRs [17].

Since a substantial proportion of ADEs can be prevented, it seems logical to focus on the preventive aspect in particular. In fact it is better to prevent than to cure. Different methods to prevent ADEs are [18,19]:

- basic computerized physician order entry (CPOE)
- CPOE with clinical decision support system (CDSS)
- a clinical pharmacist attending on physician rounds or monitoring medication ordering, transcribing and delivery
- robots in drug dispensing
- "smart" intravenous devices
- barcoding of drug and patients
- automated bedside dispensing devices
- intravenous admixture units at patient care unit
- unit based dosing

Obviously, each abovementioned method interacts in a particular part of the drug distribution chain, from prescribing, dispensing to drug use.

Although a multifaceted approach, such as that Silverman et al.[20] have described for their institution seems to be the best option to reduce preventable ADEs, two of these strategies have our special interest, namely:

- CPOE with CDSS
- clinical pharmacist activities

The review of Krahenbuhl-Melcher et al. shows that medication errors occur at all stages of the medication process but most often at the administration stage and in the drug prescription process (16.5%, range 13–74% of all errors). CPOE may be in particularly helpful to reduce such prescribing errors [8]. Since our institution uses a CPOE already, this intervention of reducing prescribing errors is of our interest. Although no randomized control trials are performed, there are investigations showing that a reduction in ADEs can be reached through the use of CPOE with CDS systems [21-23]. CDS systems can range from basic to more advanced systems. Basic CDS systems, for example, include basic dosing guidance or drug-drug interaction checking. In contrast, more advanced CDS systems can include dosing support for renal insufficiency and guidance for medication-related laboratory testing [24]. These advanced CDSS use clinical rules, algorithms, and can search for data available in electronic form, such as medication orders, patient characteristics and laboratory values [25]. A Dutch study shows that implementation of a CPOE with basic CDSS reduces certain types of medication errors (such as dosing errors and administrative and procedural errors) but a direct effect on actual patient harm was not demonstrated [26].

Hospital pharmacist participation on ward rounds is common in many hospitals and has been proven to prevent errors, to lower drug costs and to reduce ADEs in for example intensive care and general medicine units [27,28]. Limited human resources may restrict pharmacist participation on ward round teams in all of the medical units of a hospital, necessitating selection of patients at risk of ADEs [19]. Since we have a special interest in clinical pharmacist activities, but we have a limited capacity, we choose to focus on hospital pharmacist interventions guided by alerts from CPOE with CDSS.

At our institution, the site where we perform our studies, Leiden University Medical Center, a CPOE with basic CDSS is in use since 2003, as one of the first University Medical Centers in The Netherlands. This system gives basic drug-drug interaction and drug-dosing alerts and can in that way prevent some medication errors [29]. Our hypothesis is that the use of a more advanced CDSS incorporating clinical rules can better identify patients at risk of

ADEs. In addition, hospital pharmacists can interfere to prevent ADEs and, as such, improve medication safety. We choose to combine our two strategies of interest to prevent ADEs: CDSS for selecting patients at risk of ADEs and hospital pharmacist intervention focused on the specific patient at risk instead of participation on ward rounds.

The aim of this thesis is 1) to develop a CDSS with clinical rules to use in the hospital pharmacy to select patients with potential ADEs and 2) to investigate the ability of this system to select these patients at risk of ADEs and finally 3) to investigate if these potential ADEs can be prevented by interventions by the hospital pharmacist. All of these studies focus on the hospitalized patient.

This thesis starts with a comprehensive review of the literature in which an overview is presented of methods described to prevent ADEs (**chapter 2**).

The next chapter, **chapter 3**, describes the development of the CDSS with clinical rules aimed to identify patients at risk of ADEs. The system is called Adverse Drug Event Alerting System (ADEAS). Besides the development of the system and the definition of the first set of clinical rules, the validation of the system and a proof of principle test are described.

In **chapter 4 and 5** the newly developed ADEAS is compared with other methods to select patients at risk of ADEs. **Chapter 4** describes the retrospective and prospective comparison of ADEAS with the conventional medication surveillance, using a basic CDSS in the existing CPOE. In **chapter 5**, a limited set of clinical rules from ADEAS and a basic CDSS within CPOE is compared with manual pharmacist medication review.

Chapter 6 investigates the extent in which ADEAS based interventions by the hospital pharmacist can prevent ADEs in the elderly patient with polypharmacy. This study is conducted on 5 hospital wards and ADEs are scored by chart review.

The use of ADEAS with clinical rules in daily hospital pharmacy practice is evaluated in **chapter 7**. This chapter also gives an overview of the rule effectiveness and positive predictive value of the clinical rules incorporated in ADEAS.

Finally, in **chapter 8**, the development of ADEAS and the clinical rules, and the ability of the system to select patients at risk of potential ADEs and the ability to prevent these ADEs is discussed and put in perspective. This chapter also describes our ideas for future use of clinical rules in hospital practice to select risk patients, to prevent ADEs and ultimately to make drug use more safe for our patients.

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2

Preventing adverse drug events in hospital practice: an overview

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Summary

Adverse drug events (ADEs) are a considerable cause of morbidity and mortality in hospital practice. The precise frequency is unknown, but studies give an incidence number ranging from 2 until 52 ADEs per 100 patients. There are many different methods for definition, causality assessment, severity classification and detection of ADEs which make it difficult to compare the different studies. A substantial part (in some studies up to 70%) of ADEs can be prevented and it is important to, besides their detection, focus on the prevention of these ADEs. In this literature review we give an overview of methods for preventing ADEs. There are many different tools with different impact on a particular part of the distribution system which has the potential to prevent ADEs. A multifaceted approach is needed. Two interesting strategies of prevention, pharmacist participation on ward rounds and computerised physician order entry with clinical decision support systems (CDSS), are highlighted. Moreover, two promising CDSS are discussed in more detail, namely computer-based monitoring systems and information systems which link laboratory and pharmacy data.

Introduction

Drug use was the leading cause of adverse events, defined as an injury due to medical treatment, in the Medical Practice Study. These so-called Adverse Drug Events (ADEs) were accounting for 19.4% of the injuries found in this study [1]. Since then, ADEs have been a subject of intense research. There is an enormous amount of data about the incidences, detection and costs of ADEs. The precise frequency is unknown, but studies give an incidence number ranging from 2 until 52 ADEs per 100 patients [2-13].

The reported incidence figures of ADEs depend partly on different variables, such as definition, causality assessment, severity classification and detection methods. The World Health Organization (WHO) defines an ADE as 'any untoward medical occurrence that may be present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment' [14]. This definition is often simplified to the more straightforward description 'an injury resulting from the use of a drug' [3,15].

ADEs can be divided into intrinsic and extrinsic harm. Intrinsic harm is the result of the pharmacological properties of the drug itself and is also called adverse drug reaction (ADR). Extrinsic harm is related to the manner the drugs are used and is also referred to as medication error. Potential ADEs, in contrast to actual ADEs, are medication errors with the potential to cause an injury but which do not necessarily cause any injury [15,16]. Different classification methods are described in the literature, varying in simplicity from NCC MERP medication error index to just mild, moderate and severe [3,5,16-19]. Also varying degrees of causality assessment are used [14,20-22]. Methods for the detection of ADEs are voluntary report, chart review and computer-based monitoring systems [3,5,12,19,23-26].

All these variables reduce the ability to make generalisations about the data on ADEs and make it difficult to compare the studies.

Besides these limitations it is the widespread impression that ADEs in hospitals are costly and prolong hospitalisation [6,27,28]. Most adverse events, including ADEs are preventable, particularly those due to error or negligence [3]. Theoretically, increasing the knowledge on ADEs and its understanding may turn into a higher proportion of ADEs becoming preventable.

Since a substantial proportion of ADEs can be prevented it is important to, after the detection, focus on the prevention of ADEs. An important step in reducing the incidence of adverse events is to identify the patients at highest risk for ADEs. However, in common hospital practice it is quite difficult to decide where and how to start. With this in mind, we have

reviewed the literature to provide our overview on different useful methods of prevention of ADEs. These useful and promising tools for detecting patients at risk for ADEs may contribute to an improvement of drug safety.

Methods

A literature search using Pubmed was performed to search for articles published between 1990 and February 2007. The search was done using the terms 'adverse drug events' in combination with 'prevention' and 'hospital'. The reference sections of all retrieved articles (in English) were manually searched for additional articles. Publications covering ADEs encompassing either medication errors and/or adverse drug reactions were included. Papers covering outpatient problems were excluded because we focus on hospital prevention of ADEs. Rather than exhaustively reviewing the literature on this topic, we selected papers that reflect exemplary current practice and suits our abilities and interest in relation to CPOE and CDSS and pharmacist ward participation as strategies to prevent ADEs.

Prevention of ADEs

Obviously, ADEs form an important and costly problem in the current health care system. As a considerable part of the ADEs are considered preventable, it seems logical to approach this problem by focusing on the preventable ADEs. In order to prevent ADEs it is important to detect them first. However, it is less clear where and how to start in a complex health care environment with a variety of clinical fields, medical professionals, types of patients and therapeutic options.

In a system analysis of ADEs, Leape et al. [29] found 16 major system failures as the underlying causes of the errors. The most common system failure was in the dissemination of drug knowledge, particularly to physicians, accounting for 29% of the errors. Physicians made many prescribing errors that appeared to be due to deficiencies of knowledge of the drug and how it should be used. These included incorrect doses, dosage forms, dosage regimens and routes of administration, as well as errors in the choice of drugs. The systems for verifying that the proper drug is delivered in the proper dose sometimes failed in both the pharmacy at dispensing and nursing at administrating the drug. A significant cause of identity errors was look-alike packing and sound-alike names for drugs. Inadequate availability of patient information was associated with 18% of errors. Information about the patients' condition, results of laboratory tests, current medications and recent doses were

sometimes not easily accessible when it was needed, leading to prescribing errors as well as inappropriate administration of ordered drugs. Pharmacists sometimes lacked information about clinical characteristics of patients and results of laboratory tests that would have enabled them to intercept an improper order. Other system failures were order transcription, allergy defence, medication order tracking and interservice communication [29]. Bates et al. [30] proposed a risk stratification model for patients likely to experience an ADE using a cohort analysis and a case-control study. However, almost none of the proposed 'risk factors', such as age, multiple drug therapy and impaired renal function, were actually associated with a substantially elevated risk of developing an ADE. No major drug class was responsible for a disproportionate share of the ADEs, with the possible exception of analgesics. They concluded that rather than targeting patients at high risk of experiencing an ADE, prevention strategies should focus on improving medication systems [30], for example implementing a patient safety program [30-32] or performing risk assessment with multidisciplinary teams [33]. In a paediatric setting, Fortescue et al. [34] analysed 10 medication error prevention strategies for their potential effectiveness in reducing both overall error rates and potentially harmful error rates. These10 strategies included: (1) basic computerised physician order entry (CPOE); (2) CPOE with clinical decision support systems (CDSS) including checks of drug ordering and patient factors; (3) a clinical pharmacist on physician rounds or monitoring medication ordering, transcribing and delivery; (4) changes in communication; (5) computerised medication administration records; (6) robots in drug dispensing; (7) 'smart' intravenous devices for performing dilutions; (8) barcoding of drugs and patients; (9) automated bedside dispensing devices and (10) unit-based dosing. They found that three interventions might have prevented 98.5% of all potentially harmful errors being CPOE with CDSS, ward-based clinical pharmacists monitoring ordering, transcribing and administering and improved communication among physicians, nurses and pharmacists [34].

A study from Evans et al. [35] was designed to identify inpatient risk factors for ADEs. Conditional logistic regression was used to analyse all pharmacist-verified ADEs by therapeutic class of drugs and severity during a 10-year study period in a 520-bed teaching hospital. Each case patient was matched with up to 16 control patients. They found four classes of drugs causing the majority of the ADEs: analgesics, anti-infectives, cardiovascular agents and anti-coagulants. They also showed that female gender was a uniformly significant risk factor for ADEs, while age was not. Creatinine clearance was a prominent risk factor only in the cardiovascular drug category. Increased dose, number of co morbidities and parenteral routes of administration were found to be a significant risk factor for ADE in nearly every drug category. They conclude that the four high-risk drug classes should be

closely monitored based on patient characteristics (gender, age, weight, creatinine clearance, number of comorbidities) and drug administration (dosage, administration route, number of concomitant drugs) [35].

Clearly, there are many different tools which have the potential to prevent ADEs but with different impact. Each tool has its impact on a particular part of the drug distribution system, for example barcode scanning of drugs and patients will only prevent administration errors and not other kinds of ADEs. Thus, a multifaceted approach, such as that Silverman et al. [36] has described for their institution, seems to be the best option to reduce preventable ADEs.

Two strategies of such a multifaceted approach to prevent ADEs we have special interests in and will be highlighted. These interventions are: (1) pharmacists participation on ward rounds and (2) CPOE with CDSS. Two of these CDSS we are working on as well and are discussed in more detail, namely (A) computer-based monitoring system with alerts and (B) linking laboratory and pharmacy information systems.

Pharmacist participating on ward rounds

Fortescue et al. [34] proposed clinical pharmacists on ward rounds as a potential strategy to reduce ADEs. Leape et al. [37] conducted a controlled clinical trial to estimate the effect of pharmacist participation on medical rounds in the ICU on the rate of preventable ADEs caused by medication ordering errors. During a 6 month period in a large urban teaching hospital a senior pharmacist participated on rounds with the ICU team and remained in the ICU for consultation in the morning and was available on call throughout the day. The rate of preventable prescribing ADEs decreased by 66% from 10.4 per 1000 patient days (95% CI, 7–14) before the intervention to 3.5 (95% CI, 1–5; $p < 0.001$) after the intervention. In another unit, which served as a control, the rate was essentially unchanged during the same period. The pharmacist made 366 recommendations related to drug ordering, of which 362 (99%) were accepted by physicians. The recommendations varied from clarification or correction of the medication order, provision of drug information to recommendation of alternative therapy and identification of drug–drug interactions [37]. Similarly, Kucukarslan et al. [38] studied during a 3 month period the effect of pharmacists on rounding teams in a general medicine unit. The services of the clinical pharmacist included rounding, documenting pharmacotherapy history and providing discharge counselling. The rate of preventable ADEs was reduced by 78%, from 26.5 per 1000 hospital days to 5.7 per 1000 hospital days. They documented 150 interventions, of which 147 were accepted by the team. The most common interventions were dosing-related changes and recommendations to add a drug to

therapy [38]. A systematic review of Kaboli et al. [39] evaluated the published literature on the effects of clinical pharmacist interventions in controlled trials in hospitalised patients. In 36 studies, three different types of clinical pharmacist services were reviewed: (1) patient care unit pharmacist participation on rounds (10 studies); (2) admission or discharge medication reconciliation (11 studies) and (3) drug class-specific pharmacist services (i.e. inpatient anti-coagulation services, antibiotic therapy and infectious disease counselling and therapeutic drug monitoring services; 15 studies). Different outcome measures were used. For example 7 of 12 studies reported a reduction of ADEs, ADRs or medication errors and 5 reported no differences. Hospital length of stay was reduced in 9 of 17 trials and readmission rates, ICU transfers, test use and costs were either reduced or not affected. Mortality was evaluated in eight trials. One showed a significant reduction. Of the other seven studies, three demonstrated lower mortality and four demonstrated higher mortality in the intervention group, but these differences were not significant. The overall conclusion was that the addition of clinical pharmacist services in the care of the inpatients generally resulted in improved care, with no evidence of harm [39]. Finally, in a 84 beds paediatric academic setting, Wang et al. [40] quantified the harmful medication errors and ADEs that occurred during a 3 month period and judged whether or not these were intercepted by the clinical pharmacist system and if not whether it would have been captured by CPOE. They found 865 medication errors, including 687 non harmful medication errors, 162 near misses and 16 preventable ADEs, and also 36 non preventable ADEs. Of all potential harmful medication errors 54% were intercepted by the clinical pharmacist system. This included 78% of prescribing errors but none of the administration errors. An idealised paediatric CPOE with CDSS could capture additional prescribing errors (78% vs. 93%; $p = 0.002$), but not administration errors [40].

The positive effect of pharmacist participation on rounds on improving medication safety is obvious; however, data on cost effectiveness are currently lacking. In the study of Leape et al. the total commitment of the clinical pharmacist was approximately half of the pharmacist's time [37]. This means that having clinical pharmacists available on all hospital wards may be unrealistic also because of shortage in pharmacists in many countries.

CPOE with CDSS

One intervention that has our interest and has substantial potential for improving the medication ordering process is CPOE in which physicians write orders online [41,42]. It has been recommended by the Leapfrog group as one of the first leaps to be implemented as a major step to improve patient safety in the USA [43]. CPOE ensures complete, legible, standardised

and clear orders. CDSS are built into almost all CPOE systems to varying degrees and have the ability to improve patient safety. Basic clinical decision support provides computerised advice regarding drug dose, routes and frequencies, and more sophisticated CDSS can perform drug allergy checks, drug-laboratory value checks and drug–drug interaction checks and can provide reminders about corollary orders or drug guidelines [44-46]. In his systematic review Kaushal et al. [44] evaluated five studies regarding CPOE with CDSS. Of these studies two demonstrated a marked decrease in the serious medication error rate, one an improvement in corollary orders, one a prescribing improvement in dose and frequency of drugs and one an improvement in dose and frequency prescription of nephrotoxic drugs. For example, two studies from Bates et al. [47,48] showed a 55% and 86% decrease in preventable and non-intercepted potential ADEs, respectively. The first study showed a decline from 10.7 events per 1000 patient days to 4.68 events ($p = 0.01$). The rate of ordering errors decreased 19% overall, the number of transcription errors fell by 84% and the rates of dispensing and administration errors fell by 68% and 59%, respectively [47]. The event rate in the second study fell from 7.6 per 1000 patient days to 7.3 per 1000 patient days after implementing CPOE and further to 1.1 per 1000 patient days after improving drug allergy checking, potassium ordering and drug–drug interaction checking [48]. A more recent study in the ICU, conducted during a 5 week period, comparing two paper-based units with one unit with CPOE, found a relative reduction of 86.7% for all types of errors associated with medication ordering. The incidence of non-intercepted potential ADEs and ADEs together was significantly lower in de CPOE unit ($n = 23$) compared with the paper-based unit ($n = 60$) [49]. However, there have also been some negative reports on CPOE. Han et al. found an unexpected increase in mortality coincident with CPOE implementation [50]. Moreover, Koppel et al. [51] reported that a widely used CPOE system facilitated 22 types of medication error risks, mainly systems integration failure and human-machine interface flaws, and as Wang et al. [40] judged, CPOE captures mostly prescribing and transcription errors, but not administration errors.

Overall, CPOE has many benefits beyond medication safety and is a useful tool to prevent ADEs. It is good to realize that not every CPOE (with CDSS) is the same and that there are important differences between the systems used in different countries. Overall, it is here to stay, but needs continuous monitoring and fixing [52].

Computer-based monitoring system with alerts

One example of CPOE with CDSS to prevent ADEs is the use of computer-based monitoring systems, also called clinical event monitoring systems or clinical event monitors. These systems can use any data available in electronic form to detect adverse drug events. These

can be administrative data, like coded data (ICD-9-CM), free text trigger words, drug prescription, or multiple data like combination of sources using queries, rules or algorithms [19,23,24,53]. We focus on systems that monitor clinical laboratory data, demographic patient data and physician orders within a CPOE system by using defined clinical rules. These clinical rules or algorithms are based on identifiers searching for specific medication orders, patient characteristics and/or laboratory values [5,25,54,55].

Raschke et al. [54] developed a computer alert system to correct errors that might lead to ADEs and to detect ADEs before maximum injury occurs. In a prospective case series 37 drug-specific ADEs were targeted. During the last 6 months of 1997 the alert system fired 1116 times and 596 (53%) were true-positive alerts (defined as in which the physician wrote orders consistent with the alert recommendation). The alerts identified opportunities to prevent patient injury secondary to ADEs at a rate of 64 per 1000 admissions [54]. Likewise, Silverman et al. [55] used a computer-based detection system with rules that identify actionable events (excluded identification of ADE after it has occurred). In 3 different periods they used 58 rules and performed 169, 452 and 792 interventions based on these rules respectively. The rules were continually assessed by evaluating the positive predicted value. Of these interventions by pharmacists, 133 (78.7%), 411 (90.9%) and 730 (92.2%) were accepted by the physician in each period, respectively. The most efficient rules in terms of intervention were a quinidine level above 5 mg/dl and a theophylline level above 20 mg/dl [55]. It is essential that the CDSS provide the user with relevant guidance regarding prescribing and monitoring decisions without overwhelming the user with irrelevant alerts; if too many low-level alerts are delivered, prescribers may disregard important warning messages [56]. A problem that might occur with CDSS is 'alert fatigue'. In their review, Van der Sijs et al. [56] mention that in 49% to 96% of cases, drug safety alerts in CPOE are overridden by clinicians. They warn for error-producing conditions of the alert system, like low specificity, low sensitivity, unclear information content, unnecessary workflow disruptions and unsafe and inefficient handling. One explanation may be that medication control is one of the tasks of the complex function of the physician, whereas medication control is the core business of the pharmacist. Therefore a broader range of warnings can still be displayed to the pharmacist, for example after prescribing but before dispensing.

Linking laboratory and pharmacy information systems

Many of the clinical rules used in computer-based monitoring systems consist of a combination of drug and laboratory algorithms. Laboratory and pharmacy functions are closely related. Drug choice and dosing often depend on laboratory information such as

therapeutic drug levels and biochemical and other physiologic parameters. Despite this relation between laboratory and pharmacy, connection between their information systems is often suboptimal or non-existent [57]. ADEs that may be prevented by use of such a CDSS are for example wrong dosing of drugs which are eliminated by the kidney in patients with impaired renal function [58,59], prescribing potassium to patients despite high plasma potassium level [60] and lack of monitoring at initiation of drug therapy [61]. Several studies have demonstrated that drug- laboratory combinations are one of the best tools for identifying (potential) ADEs [5,19,25,62]. Schiff et al. [57] describe in their review 10 ways in which laboratory and pharmacy data can be related to improve patient care. Their knowledge-based rules are for example linking laboratory findings with drug selection (indication or contraindication), with drug dosing, drug use with laboratory monitoring for toxicity and also drug use and interference with laboratory measurements. The linking between tests and treatments can be retrospective, linking downloaded laboratory and pharmacy files, or real-time via CPOE with CDSS [57].

Information technology can reduce the frequency of ADEs. The main classes of strategies for this prevention include tools that can improve communication, make knowledge more readily accessible, require key pieces of information, perform checks in real time, assist with monitoring and provide decision support. However in today's systems, many important warnings are ignored and there are too many unimportant warnings. Thus, pre-screening by the pharmacist can be useful [45,63].

Conclusion

ADEs in hospital practice cause considerable morbidity and even mortality albeit its precise frequency is yet unknown. Since a substantial proportion of the detected ADEs can be prevented we find it important to focus on the prevention of ADEs. It is suggested to follow a systems approach, involving multiple strategies, such as CPOE with sophisticated CDSS and patient-oriented pharmacy services, to adequately encounter the problem of ADEs in hospital settings. Linking pharmacy and laboratory data is a good way to start. Information technology can be very helpful to reach this goal.

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Part II

Analytical validity

3

Development of a computerised alert system, ADEAS, to identify patients at risk of an adverse drug event

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Abstract

Introduction: Adverse drug events (ADEs) are frequent and pose an important risk for patients treated with drugs. Fortunately, a substantial part of ADEs is preventable, and computerised physician order entry with a sophisticated clinical decision support system may be used to reach this goal.

Objective: To develop a new system that could improve the quality of medication surveillance. The system should focus on detecting patients at risk of an ADE by combining data from the hospital information system and computerized physician order entry (drug prescription data, drug-drug interaction alerts, clinical chemical laboratory parameters, demographic features), using clinical rules.

Methods: The clinical rules were formulated in a multidisciplinary team based on seven risk categories. The new system was composed in a guideline-based decision support framework consisting of both a guideline development module and a decision support module. A total of 121 clinical rules were built into the system. Validation of the system and a proof of principle test were performed.

Results: The adverse drug event alerting system (ADEAS) was developed and validated successfully. The proof of principle test showed that ADEAS has potential usefulness. ADEAS generated alerts and detected additional potential risk situations, which were not generated by conventional medication surveillance.

Conclusion: We developed a pharmacy decision support system ADEAS that focusses on the detection of situations prone to lead to an ADE and might help clinicians to take timely corrective interventions and thereby can prevent patient harm.

Introduction

Adverse drug events (ADEs) and medication errors pose a serious risk for hospitalised patients. A recent review shows that medication errors occur in about 5% (range 0.038%–56.1%) of all episodes of drug administration and that ADEs occur in about 6% (range 0.17%–65%) of hospitalised patients. About 46% (range 15%–90%) of ADEs, mainly those resulting from medication errors, appear to be preventable [1]. A reasonable approach to increase patient's safety is to focus on the prevention of ADEs by identifying patients at highest risk for development of an ADE. Computerised physician order entry (CPOE) combined with a sophisticated clinical decision support system (CDSS), including usage of electronic pharmacy and laboratory data, can be used to detect those patients at risk of an ADE [1-3]. Potential risky situations can be defined in clinical rules [4,5]. This approach would permit physicians and pharmacists to take corrective actions before harm occurs.

In our hospital, the CPOE system in use provides online drug–drug interaction checks and drug-dosing checks but is not integrated with a sophisticated CDSS [6]. This current surveillance system has some limitations: 1) there is no possibility to adapt medication surveillance to categories of patients and/or to medical specialities, [7] 2) the system does not take into account relevant laboratory values, and 3) most alerts are of low clinical relevance with the consequence of 'alert fatigue' [8].

Given these limitations and the wish for more clinical pharmacy activities, we aimed to develop a new pharmacy decision support system that could improve the quality of our medication surveillance. The system should focus on patients at risk of an ADE by combining more data available from the hospital information system and CPOE, using clinical rules.

In this context, we describe the development of our computerised alert system, adverse drug event alerting system (ADEAS).

Methods

Setting

Leiden University Medical Center is a university hospital in Leiden, The Netherlands. The hospital information system, Mirador (iSOFT Nederland, Leiden, The Netherlands), contains integrated patient-specific data, including demographics, laboratory results, discharge letters, diagnosis, surgery reports, radiology reports and pharmacy orders. The CPOE system in use, Medicator (iSOFT Nederland), provides online, during prescribing, drug–drug interaction

checks and drug-dosing checks but is not integrated with a sophisticated CDSS [6]. The safety alerts in the CPOE system are based on a national drug information database, the G-standard (Z-Index, The Hague, The Netherlands). The G-standard contains information about all drugs (approved and none approved) available in The Netherlands, and the majority of Dutch pharmacy information systems use this database to support different processes such as medication surveillance.

Current procedure of our conventional medication surveillance is that hospital pharmacists perform daily retrospective checks of the drug–drug interaction and drug-dosing alerts overridden by the physician during prescribing. The hospital pharmacist selects potentially clinical relevant alerts to discuss with the prescribing physician by phone. Additional dosing advice is given following therapeutic drug monitoring results.

Description of the system

The development process of the new system can be subdivided into four phases: 1) the definition of the contents of the clinical rules, 2) the development of expert system itself (ADEAS), 3) building of clinical rules into ADEAS and 4) technical validation (see flowchart, Figure 3.1).

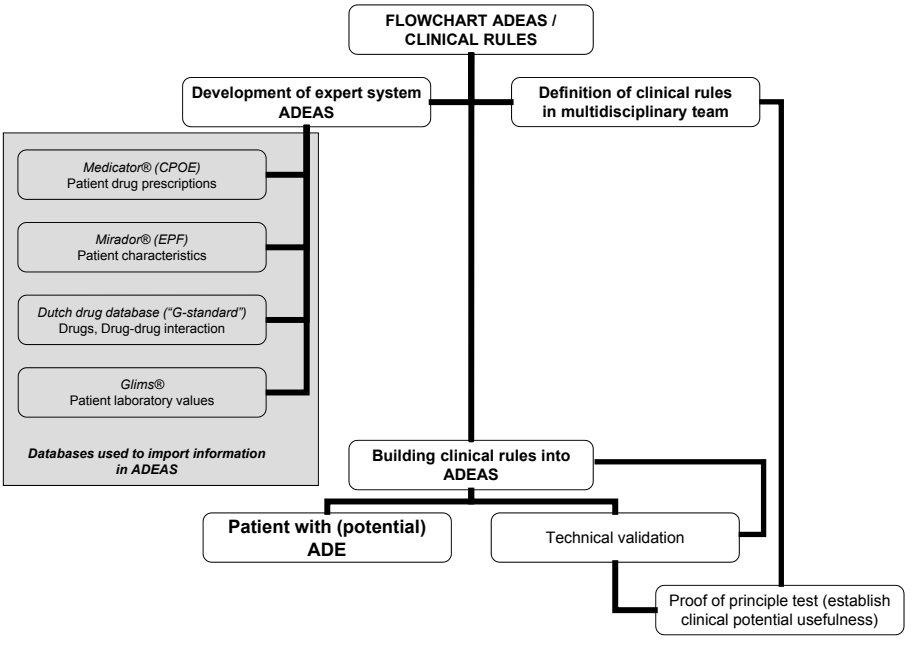

Figure 3.1 Flowchart development ADEAS / clinical rules.

Definition of clinical rules

First, we have put together a multidisciplinary team including a pharmacist, a hospital pharmacist, an internal medicine specialist and a hospital pharmacist-clinical pharmacologist, to discuss the contents of the clinical rules. We used the Dutch national formulary (Farmacotherapeutisch Kompas, College voor zorgverzekeringen, Diemen, The Netherlands) and local medical reference books (e.g., hospital antibiotics formulary) to identify drugs or drug classes suitable for use in a clinical rule. From a drug perspective, we used seven risk categories to formulate the clinical rules (Table 3.1). For each drug or drug class, the seven risk categories were discussed in the multidisciplinary team and finally resulted in agreement and definition of various clinical rules. An example of a rule for each risk category is given in Table 3.1. We did not formulate clinical rules for anticancer drugs because ADEs related to these agents are frequent, well recognised, intensively monitored but difficult to fully prevent. Moreover, for prescribing anticancer drug regimens, the CPOE system already assists the physician by applying chemotherapy prescription protocols [7]. Overall, we defined about 300 clinical rules.

Table 3.1 7 risk categories which are used to define clinical rules from a drug perspective

1	Linking biochemical laboratory values with the initiation of a drug *example: patient with aminoglycoside or vancomycin and plasma creatinine unknown last 7 days before start*
2	Linking biochemical laboratory values or therapeutic drug monitoring values with the ongoing use of a drug *example: patient with SSRI and platelets < 100 x 10^9/L or platelets drop > 25%*
3	Linking the use of a drug with the non-use of another drug the latter indicated for the prevention of an ADE *example: patient with opioid receptor agonist and no laxative within 2 days after the prescription of the opioid receptor agonist*
4	Medication used to treat an ADE *example: patient with ACE inhibitor and codeine or anti-cough medication*
5	The history of our currently used medication surveillance system fine-tuned to risk-patients *example: patient (> 60 yr) with low dose aspirin or NSAID (except COX-2 inhibitor) and CHF without ulcer protection*
6	Alert from inspectorate authorities such as EMEA or company regarding an ADE and/or special considerations for use from product label *example: patient with azathioprine (alert from Dutch inspectorate authority that dose check related to patient weight is required for this drug)*
7	Common medication errors, including alerts from the Dutch CMR (Central Medication Error Registration) *example: patient with methotrexate once daily instead of once weekly*

ADE, adverse drug event; COX, cyclooxygenase; CHF, congestive heart failure; EMEA, European Medicines Agency; SSRI, Selective serotonin reuptake inhibitor.

Development of the CDSS (ADEAS)

Second, we built the expert system itself. ADEAS was composed in Gaston (Medecs, Eindhoven, The Netherlands), a guideline-based decision support framework consisting of both a guideline development module and a decision support module [9,10]. The guideline development module consists of a Task Network Module [11] that describes the structure ('logic' or 'flow') of the guideline by means of a set of primitives (such as observations, decisions, actions) and domain-specific knowledge in the form of one or more terminologies. We defined the following terminologies: drug, laboratory values, drug–drug interactions and patient characteristics. The data for the 'drug' and 'drug–drug interaction' sections were imported from the national drug information database, the G-standard. The data regarding laboratory values and patient characteristics were imported from the hospital information systems, Glims (MIPS Diagnostics Intelligence, Clinisys, UK) and Mirador. The information about the drug use of a specific patient was imported from the CPOE, Medicator (Figure 3.1, grey box).

The decision support module was used to link Gaston with our hospital information system for importing the required information and to execute the clinical rules. Gaston was originally designed as a CDSS, but we wanted to use ADEAS as a pharmacy decision support system instead, thus technical adaptations were made to the reporting technology.

Building clinical rules into ADEAS

The primitives and terminologies were combined and used to create and build the clinical rules into the system (Figure 3.2). The items were dragged to the desired field (positive or negative preferences). Per terminology item, sub items such as dosages or administration route for a drug could be added. Most clinical rules consisted of simple observations of one or more positive and/or negative term preferences, for example, a drug prescription and the presence of a laboratory value (Figure 3.2) or a drug prescription and the absence of a laboratory value. More complicated clinical rules were built as a flowchart (Figure 3.3).

Of the about 300 clinical rules defined, we finally incorporated 121 clinical rules in the system (Appendix). These clinical rules were chosen because they were considered most relevant to our hospital practice.

Validation

After building the clinical rules into ADEAS, we performed a validation to establish the technical correctness of the system. It is necessary to investigate that the system adequately detects patients described in the intended situations in the clinical rule. In other words, the

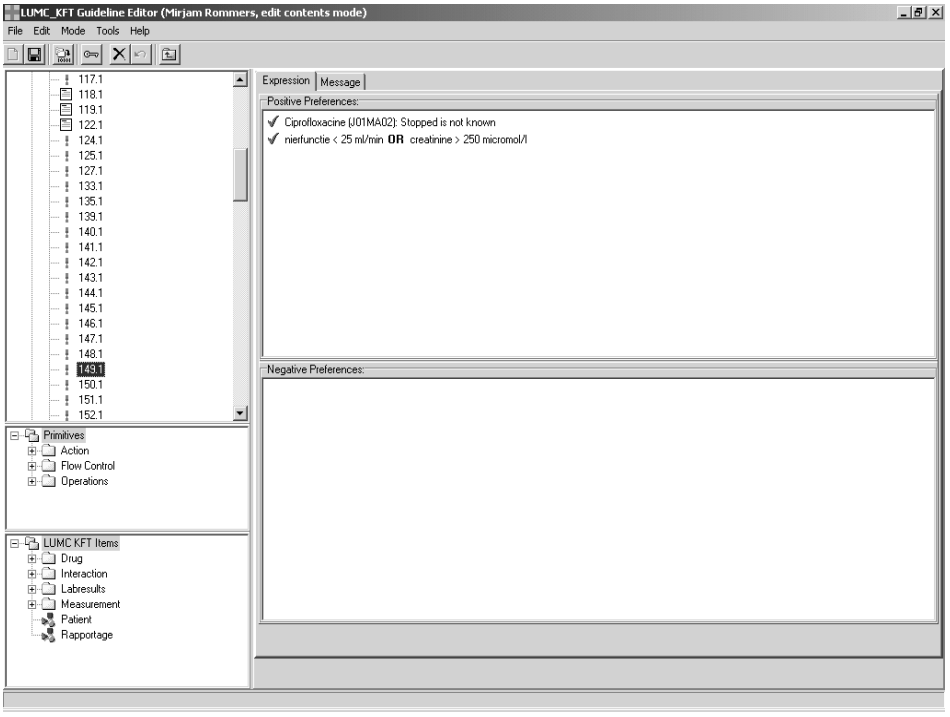

Figure 3.2 Adverse drug event alerting system (ADEAS) clinical rule consisting of two positive term preferences: drug prescription of ciprofloxacin is known and creatinine clearance is < 25 ml/min or plasma creatinine exceeding 250 µmol/l.

system should not generate false positive or false negative alerts. The correct performance of the system depends on the way the clinical rules are built in ADEAS, thus in the way the primitives and terminologies are used to create the rule or flowchart. Looking at our rules, we established that we had used 45 different technical ways of building and describing a rule in ADEAS, for example, rules consisting of only a positive term 'drug', rules consisting of a positive term 'drug' and a positive term 'laboratory value, creatinine value', individual flowcharts, rules consisting of a positive term 'drug' and a dosage limitation, etc. We divided all rules in the 45 different groups, and instead of validating each separate clinical rule, we selected one representative rule of each group for validation. The validation of that rule was representative of the rest of the clinical rules in the group. We considered it allowed to perform the validation in this way because ADEAS imports its data from already validated subsystems (Mirador, Medicator, etc). We used three different methods for the validation: A) use of dummy patients, B) in an off-line test setting, and C) behind-the-scene testing.

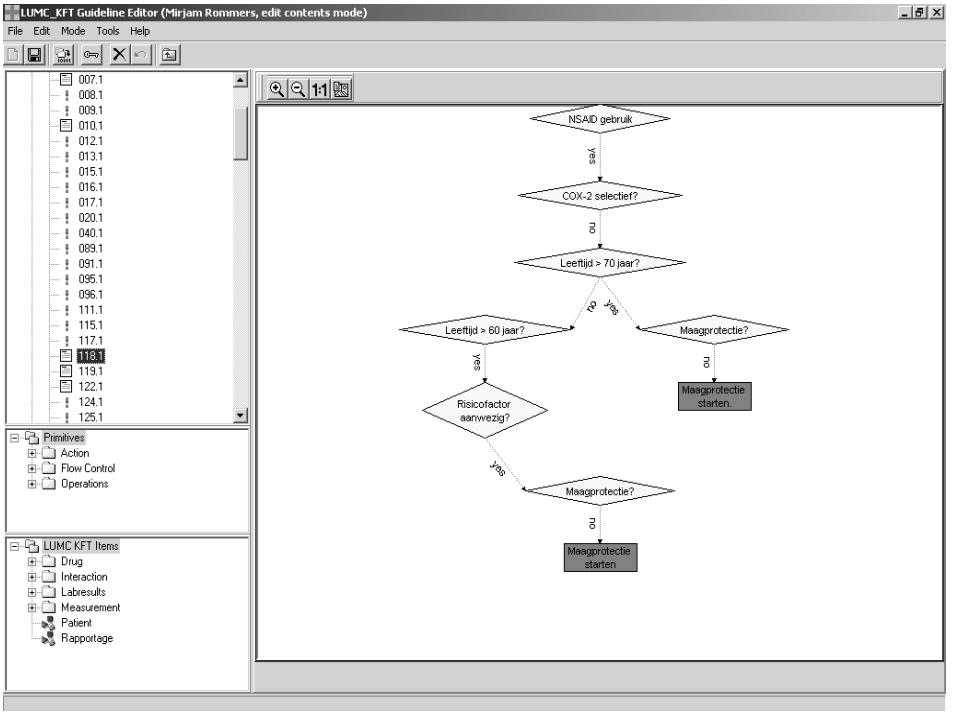

Figure 3.3 Adverse drug event alerting system (ADEAS) clinical rule consisting of a flowchart (combination of primitives and domain-specific terms). Every primitive contains one or more positive or negative term preferences.

A. Based on the content of the defined clinical rules, we entered medication orders in the CPOE for non-existing (dummy) patients. These dummy medication orders should either generate an alert (positive control: e.g., prednisolon and ibuprofen in an 80-year-old patient without a proton pump inhibitor) or not generate an alert (negative control: e.g., prednisolon and ibuprofen and pantoprazole in an 80-year-old patient). The output of ADEAS was compared with the intended output based on the entered medication combinations. Since dummy patients do not have clinical laboratory data in their hospital information system, this way of validation is only suitable for clinical rules based on medication data alone.

B. Clinical rules based on laboratory values were tested in existing patients in an off-line test setting. We selected patients with required laboratory values and entered medication in an off-line setting in the same way as described above. Again, we compared the output of ADEAS with the expected output based on the combination of entered medication and laboratory values.

C. Finally, in the behind-the-scene validation method, ADEAS was run in the central pharmacy, behind the scene, on a selected group of clinically admitted patients. The electronic patient file of the patient was checked manually to compare the output of ADEAS with the expected output and to search for false negative results.

During the validation, the structure of the clinical rules was changed and adapted until testing resulted in no more false negative or false positive results. We did not calculate the sensitivity and specificity in numbers because we considered the technical validation as part of the development.

Study design

Following the development of ADEAS, we performed a proof of principle test (see flowchart, Figure 3.1). This test was performed to establish the potential clinical usefulness of ADEAS. For the test, we activated 13 different clinical rules, at least one rule of each risk category (Table 3.2). We choose these 13 clinical rules for two reasons: 1) the situations described in

Table 3.2 Results proof of principle study of ADEAS with 13 clinical rules active processing during 3 days

Clinical rule	No. patients
Patient with aminoglycoside or vancomycin and plasma creatinine unknown last 7 days before start	0
Patient with SSRI and platelets < 100 x 10^9/l or platelet drop > 25%	0
Patient with nitrofurantoine and CL < 50 ml/min*	0
Patient with opioid receptor agonist and no laxative within 2 days after prescription of opioid receptor agonist	45
Patient with ACE inhibitor and codeine or anti-cough medication	1
Patient (> 70 yr) with low dose aspirin or NSAID (except COX-2 inhibitor) or patient (> 60 yr) with low dose aspirin or NSAID (except COX-2 inhibitor) and additional risk factor for bleeding without ulcer protection	17
Patient with azathioprine	6
Patient with 5-HT1 serotonin receptor agonist or ergotamine	1
Patient with plasma creatinine > 150 µmol/l	36
Patient with CL < 50 ml/min*	21
Patient with plasma creatinine rise > 50%	11
Patient with plasma creatinine rise > 50 µmol/l	10
Patient with CL decline > 50%*	1

* CL, creatinine clearance.

these rules are highly prevalent and 2) the situations described present relatively high-risk situations prone to lead to patient harm [12-14]. During 3 days, ADEAS was processing every night collecting new patients and data from the electronic patient file of all admitted patients to the hospital at that time. The amount and contents of the alerts generated with ADEAS was compared retrospectively with the alerts and interventions that resulted from the conventional medication surveillance in the same period. This was done to assess the potential additional value of ADEAS compared with our current medication surveillance. The positive predictive value of the clinical rules was not calculated because we did not register the actions made by the pharmacist or physician following an alert from ADEAS.

Results

During the three days of the proof of principle test, on average, 400 patients were admitted to the hospital per day. ADEAS, with 13 active clinical rules, generated 149 alerts covering 116 patients (Table 3.2). Of these alerts, 20 were related to a declined renal function. In the same period, the conventional medication surveillance system generated 308 alerts (on average 100 alerts per day) in 240 different patients. In only 6% (n = 20) of these alerts, the pharmacist retrospectively contacted the physician to give additional advice about separate administration of drugs (n = 10), ECG monitoring (n = 4), therapeutic drug monitoring (n = 5) or adding additional medication (n = 1). The alerts generated with ADEAS regarding a declined renal function were not generated as safety alerts within the CPOE. The conventional medication surveillance generated drug–drug interaction alerts between a non-steroidal anti-inflammatory drug and a corticosteroid, even when a prescription of a proton pump inhibitor (PPI) was present. ADEAS only selected the situations a PPI was absent. ADEAS also selected situations in which low-dose aspirin was prescribed to patients > 70 years of age. The conventional medication surveillance only selected these situations when a drug–drug interaction with low-dose aspirin was present in a patient with that age.

Discussion

We developed a pharmacy decision support system (ADEAS) that is able to electronically detect patients with potential riskful situations of an ADE described in clinical rules. Combined data from the CPOE, the hospital information system and the national drug information database are used as the source of information.

The definition of the clinical rules was done by a multidisciplinary team using a national formulary. We applied a structured method using seven risk categories to define the clinical rules. This method resulted in a large set of clinical rules with a wide clinical coverage. The technical validation revealed that the system is able to correctly identify patients in situations described in the clinical rules. The proof of principle test showed that ADEAS has clinical useful potential.

A strength of ADEAS is that it combines data from different databases available in the hospital. Especially, the possibility to use laboratory data (e.g., declined renal function) is of large added value [15]. Other areas such as microbiology and medical diagnosis were not included because coded data on that area were not available. The result of the proof of principle test showed that ADEAS generated different kinds of alert compared with the conventional medication surveillance. On the other hand, not all safety alerts from the G-standard within the CPOE were built in ADEAS. This means that for now, the two systems are both used next to each other until further development takes place.

Originally, most studies used clinical rules as triggers to identify ADEs that have already occurred. In these studies, commonly used triggers include a toxic serum drug level or a prescription of an antidote [15-21]. A limitation of these rules is that they identify ADEs that already resulted in harm and thus lack the opportunity to prevent harm. ADEAS agrees with the current idea to use clinical rules to detect patients at risk of an ADE. Like others, ADEAS selects evolving unsafe situations in which generated alerts permit physicians or pharmacists to make timely corrective interventions [4,5,12,14,22]. Silverman et al. showed that after modification of their clinical rules from detecting actual ADEs to identifying potential ADEs, the total number of interventions by the pharmacists increased, and the rules became more efficient [23].

There are some limitations of ADEAS. First, the development of the system itself was time-consuming and needed a large amount of technical support. Currently available CPOE systems on the Dutch market are not integrated with CDSS, and of the few CDSS available, such as Gaston, none matches the exact specifications essential for the application as described here. This was the reason technical adaptations were necessary. This might make it difficult to replicate for other institutions, but currently, two other university hospitals in The Netherlands have started using this system. Although similar computerised alert systems were developed in the United States [24] and Europe [25], they are not available in The Netherlands. There is very limited experience with the development of such systems among Dutch hospital pharmacies, and we are one of the first to report so.

Second, ADEAS is developed as a pharmacy decision support system and not as a CDSS within the CPOE. The alerts generated by the system go to the pharmacist and not directly to the prescribing physician. The reason for this is that we want to use ADEAS as a tool for the hospital pharmacist for more clinical ward-based activities. Following an alert from ADEAS, the pharmacist can visit the ward and consult with the physician to discuss the clinical relevance of the potential ADE situation. Also, we believe that pre-screening of safety alerts by the pharmacist is useful to prevent alert fatigue with the physician [24,26]. A review from Van der Sijs et al. showed that in 49%–96% of all cases, physicians ignore safety alerts. This can lead to error-producing situations; the physician does not recognise a really clinical relevant and important alert [8]. Medication control is the core business of the pharmacist, and it is suggested that the prescribers' knowledge of potential clinically relevant drug–drug interactions is generally poor [27]. Especially in the starting period when the clinical rules might need adaptation, it is useful to see the alerts in the pharmacy. In the future, some alerts might be better situated as online alerts for the physician when immediately action is necessary.

Finally, in this study, we did not establish the clinical relevance and positive predictive value of the rules. This is important and will be done in the future. In this light, it may be more efficient to start with a small set of clinical rules covering a specific clinical area (e.g., drug dosing in patients with a declined renal function) [12,14] instead of a large set, as we did.

In conclusion, we succeeded in developing a pharmacy decision support system ADEAS, which is able to electronically detect patients at risk of an ADE and might help clinicians to take timely corrective interventions and thereby prevent patient harm.

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Appendix

Clinical rule	Action	Risk category
Patient with cyclosporin and enzyminhibitor and no cyclosporin druglevel within 4 days or cyclosporin druglevel > 400 µg/l	Check cyclosporin druglevel or adapt dose	1,2
Patient with loop diuretic and start with NSAID and CHF or CL < 50 ml/min or plasma creatinine rise > 50% or > 50 µmol/l or Na < 130 mmol/l or loperamide	Switch NSAID to acetominophen or tramadol	5
Patient with opioid receptor agonist and partial opioid receptor agonist or opioid receptor antagonist	Avoid combination	5
Patient with non-selective beta blocker agent (except sotalol and carvedilol in dose equal or < 12.5 mg) and betamimetic agent	Switch to selective betablocker agent	5
Patient (> 70 yr) with digoxin (> 0.125 mg/day) or patient (> 70 yr) with digoxin and CL < 50 ml/min or plasma creatinine rise > 50% or > 50 µmol/l or patient (> 70 yr) with digoxin and K < 3.5 mmol/l	Check toxicity digoxin	2,5
Patient with lithium and start with diuretic or ACE inhibitor or angiotensin II receptor blocker and no lithium druglevel within 3 days	Check lithium druglevel	1,5
Patient with carbamazepine and start with claritromycine or erytromycine	Check carbamazepine druglevel	5
Patient with atenolol (> 50 mg/day) and CL < 50 ml/min	Adapt dose	2
Patient with sotalol and CL < 50 ml/min	Adapt dose	2
Patient with ACE inhibitor or angiotensin II receptor blocker and NSAID and CL < 50 ml/min or plasma creatinine rise > 50% or > 50 µmo/l	Stop NSAID or RAAS-inhibitor	2,5
Patient with verapamil and strong CYP3A4 inhibitor (itraconazole, ketoconazole, voriconazole, ritonavir)	Avoid combination	5
Patient with iron (oral) and penicillamine, methyldopa, antacid or levodopa	Separated administration	5
Patient with drugs through enteral feeding tube	Check if drug can be given by this route	7
Patient (> 70 yr) with low dose aspirin or NSAID (except COX-2 inhibitor) or patient (> 60 yr) with low dose aspirin or NSAID (except COX-2 inhibitor) and corticosteroid, SSRI, clopidogrel or vitamin K antagonist without ulcer protection	Add PPI	5

Appendix continues on next page

Appendix ***Continued***

Clinical rule	Action	Risk category
Patient (> 60 yr) with low dose aspirin or NSAID (except COX-2 inhibitor) and CHF without ulcer protection	Add PPI	5
Patient with SSRI and platelets < 100 x 10^9/l or platelet drop > 25%	Possible side effect	2
Patient with bezafibrate (> 400 mg/day) and CL < 75 ml/min	Adapt dose	2
Patient with anti-Parkinson's agent and TCA, flunarizine, cinnarizine, metoclopramide, antipsychotic agent, phenytoin or valproic acid	Avoid combination	5
Patient with clozapine and leucocytes < 4 x 10^9/l or leucocyte drop > 25% or leucocytes unknown	Possible side effect? stop drug	2
Patient with aminoglycoside or vancomycin and creat unknown 7 days before start	Check creat	1
Patient with 5-HT1 serotonin receptor agonist or ergotamin	Check overuse	6
Patient with aminoglycoside or vancomycine druglevel result	Check for dose adaptation and folow up TDM	2
Patient with cefuroxim and CL< 50 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with ceftazidim and CL < 100 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with meropenem and CL < 50 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with teicoplanin and CL < 100 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with claritromycin and CL < 25 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with iron (oral) and laxative, loperamide, domperidon or metoclopramide	Possible side effect?	4
Patient with clopidogrel and platelets < 100 x 10^9/l or platelets drop > 25% or leucocytes < 4 x 10^9/l or leucocyte drop > 25%	Possible side effect?	2
Patient with resin and absorption-interacted drug	Separated administration	5
Patient with amoxicillin or amoxicillin and clavulanate potassium and CL < 10 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with aminoglycoside or vancomycin > 2 days	Check aminoglycoside or vancomycin druglevel	2
Patient (> 70 yr) with SSRI and diuretic, laxative, carbamazepine or oxcarbamazepine and Na < 130 mmol/l or Na drop > 25% or Na unknown	Possible side effect? check Na	2,5
Patient with clindamycine and CL < 10 ml/min	Adapt dose conform antimicriobial therapy formulary	2

Patient with norfloxacin and CL < 50 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with ciprofloxacin and CL < 25 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with cotrimoxazole or dapson and no folic acid	If chronic use add folic acid	3
Patient with cotrimoxazole and CL < 25 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with trimethoprim and CL < 50 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with nitrofurantoine and CL < 50 ml/min	Adapt dose conform antimicriobial therapy formulary; contra-indication	2
Patient with sulfadiazine and CL < 100 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with amoxicillin (oral) or amoxicillin and clavulanate potassium (oral) and start loperamide within 2 days	Diarrhea possible side effect? adapt dose if possible	4
Patient witht erytromycine or claritromycine and terfenadine or cisapride	Contra-indication	5
Patient with ciprofloxacin or norfloxacin and anticonvulsant	Contra-indication; if possible switch to alternative antibiotic	5
Patient (< 8 yr) with doxycycline	Contra-indication	5
Patient with opioid receptor agonist and no laxative >2 days	Add laxative if necessarry	3
Patient with ACE inhibitor and codeine or cough medication	Cough possible side effect? switch to A-II-antagonist	4
Patient with isoniazide and no pyridoxine	Add pyridoxine	3
Patient with itraconazole (oral) or ketoconazole (oral) and PPI, histamine H2 antagonist or antacid	Switch to itraconazol drank or take ketocoazol with Coca Cola	5
Patient with aciclovir and CL < 100 ml/min or CL unknown	Adapt dose conform antimicriobial therapy formulary	2
Patient with valaciclovir and CL < 10 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with ganciclovir and CL < 50 ml/min or CL unknown	Adapt dose conform antimicriobial therapy formulary	2
Patient with magnesium or aluminium containing agents and CL < 25 ml/min	If chronic use adapt dose or switch to alternative drug	2
Patient with cimetidine	Switch to ranitidine	5
Patient with ranitidine and CL < 50 ml/min	Adapt dose (max. once daily)	2
Patient with cisparide	Off the market; switch to alternative	6
Patient with misoprostol and loperamide	Diarrhea possible side effect? adapt dose or take misoprostol for meal and sleep	4
Patient with phentolamine and alizapride, minoxidil or metoclopramide	If ferrochromocytoma, contra-indication	5
Patient with mesalazine like agents and loperamide	If colitis don't treat diarrhea with loperamide	7

Appendix continues on next page

Appendix ***Continued***

Clinical rule	Action	Risk category
Patient with osmotic laxative and diuretic and digoxin and no potassium and K drop > 25% or K is unknown	Add potassium or check potassium level	2,5
Patient with mesalazine and platelets < 100 x 10^9/l or platelet drop > 25% or leucocytes < 4 x 10^9/l or leucocyte drop > 25%	Possible side effect	2
Patient with risperidon and bloodglucose > 8 mmol/l or bloodglucose rise > 25%	Possible side effect	2
Patient with acrivastine, levocetirizine or cetirizine and CL < 10 ml/min	Switch to other antihistaminic drug	2
Patient with sulfonylurea agent and CL < 10 ml/min or ALAT > 135 U/l or ASAT > 135 U/l	Contra-indication	2
Patient with metformin and CL < 50 ml/min	Contra-indication	2,7
Patient with amiodaron and TSH > 5 mU/l or < 0.4 mU/l or free-T4 < 9 pmol/l or > 24 pmol/l or TSH is unknown	Possible side effect?	2
Patient with biphosphonate and no calcium and calcium < 2 mmol/l	Add calcium or stop biphosphonate	2
Patient with thyreostatic drug and leucocytes < 4 x 10^9/L, granulocytes < 30% or neutrophils < 30%	Possible side effect? stop drug	2
Patient with NSAID and methotrexate (> 50 mg/day) and CL < 50 ml/min	Adapt dose or check methotrexate druglevel, hematological lab, liver, kidney function	2,5
Patient with methotrexate (not itrathecal) > 2 days	If RA, prescription error? Once per week	7
Patient with biphosphonate oral and iv	Stop biphosphonate oral	7
Patient with NSAID and platelets < 100 x 10^9/L	Possible side effect?	2
Patient with nitrate or platelet aggregation inhibitor and COX-2 inhibitor	Cardiovascular risk?; switch to NSAID (not COX-2 inhibitor)	5,6
Patient with acetominophen (> 4000 mg/day) > 3 days	If not on oncology department, adapt dose	5
Patient with acetominophen (equal or > 4000 mg/day) and ALAT > 135 U/L and ASAT > 135 U/L or bilirubine > 40 µmol/l	Adapt dose or switch to NSAID or tramadol	2
Patient with methotrexate and no folic acid	If RA (methotrexate once per week) add folic acid	3
Patient with allopurinol (> 200 mg/day) and CL < 25 ml/min	Adapt dose	2
Patient with benzbromaron and CL < 25 ml/min	Contra-indication	2
Patient with benzbromaron and ALAT > 135 U/L and ASAT > 135 U/L	Posible side effect? stop drug	2,6

Patient with colchicine (> 8 mg/day) and use again within 3 days	Adapt dose	2
Patient with colchicine (> 0.5 mg/day) and CL < 50 ml/min	Adapt dose	2
Patient with gout and thiazide diuretic	Contra-indication; switch to loop diuretic or betablocker	5
Patient with thiazide diuretic and CL < 25 ml/min	Switch to loop diuretic	2
Patient with verapamil (> 160 mg/day) and digoxin	If not on cardiology department, check digoxine druglevel	5
Patient with verapamil or diltiazem and beta blocker	If not on cardiology department, alert for bradycardia, hypotension and AV-node conduction disorders	5
Patient with levothyroxine and start with amiodaron	Reconsider start amiodaron	5
Patient with amiodaron and start with thyreostatic or thyreomimetic drug	Possible side effect?	4
Patient with amiodaron (> 600 mg/day) > 10 days	Loading dose max. 10 days	7
Patient with amiodaron and gabapentin, pregabalin or low dose amitriptyline	Neuropathic pain possible side ffect of amiodaron?	4
Patient with methyldopa and MAO-inhibitor	Contra-indication	5
Patient with hydralazine and CL < 25 ml/min	Adapt dose	2
Patient with azathioprine or mercaptopurien and allopurinol	Additional risk of myelosuppression; adapt dose of azathioprine or mercaptopurine to 1/4 or 1/3	5
Patient with azathioprine and mesalazine, sulfasalazine, ACE-inhibitor, cotrimoxazole, cimetidine, indometacine and no platelet, granulocyte or leucocyte check	Additional risk of myelosuppression; check hematology lab	2,5
Patient with mycophenolate-mofetil or mycophenolacid and antacid or colestyramine	Separated administration	5
Patient with disulfiram and metronidazole or isoniazide	Contra-indication	5
Patient (except neonate) with ibuprofen or indomethacine iv	Prescription error	7
Patient with mitotane and spironolacton	Contra-indication	6
Patient with antipsychotic agent or antidepressant and platelets < 100 x 10^9/L, granulocytes < 30%, leucocytes < 4 X 10^9/L	Possible side effect	2
Patient with antipsychotic agent or antidepressant and ALAT > 135 U/L and ASAT > 135 U/L or bilirubine > 40 µmol/l	Possible side effect	2
Patient with irinotecan and no loperamide	Add loperamide	3

Appendix continues on next page

Appendix ***Continued***

Clinical rule	Action	Risk category
Patient with lithium and levothyroxine or free-T4 < 9 pmol/L or TSH < 0.4 mU/L	Possible side effect?	2
Patient with lithium and start NSAID and no lithium druglevel within 3 days	Check lithium druglevel	1,5
Patient with lithium and CL < 50 ml/min	Check lithium druglevel	2
Patient with TCA and laxative or prokinetic drug	Possible side effect obstipation or stomach retention	4
Patient with azathioprine	Check dose (max. 5 mg/kg)	6
Patient with TCA and oxybutinine	Possible side effect urine retention?	4
Patient with statin and CPK > 1000 U/l or patient with statin and gemfibrozil and CPK unknown or patient with statin (except fluvastatin and pravastatin) and clinical relevant drug-drug interaction	Possible side effect? switch to alternative statin	2,5
Patient with LMWH and CL < 25 ml/min	Contra-indication; switch to UFH	2
Patient with ranitidine and platelets < 100 X 10^9/L or platelet drop > 25%	Possible side effect?	2
Patient (> 60 yr) with low dose aspirin or NSAID (except COX-2 inhibitor) and DM or RA without ulcer protection	Add PPI	5
Patient with chinolon and absorption-interacted drug	Separated administration	5
Patient with tetracycline and absorption-interacted drug	Separated administration	5
Patient with biphosphonate and absorption-interacted drug (iron, calcium, antacid)	Separated administration	5
Patient with lamivudine and CL < 50 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with foscarnet and CL < 100 ml/min	Adapt dose conform antimicriobial therapy formulary	2
Patient with gabapentin or pregabalin and CL < 50 ml/min	Adapt dose	2
Patient with CL < 50 ml/min or plasma creatinine > 150 µmol/l	Check for risk drugs	7
Patient with plasma creatinine rise > 50% or > 50 µmol/l	Check for risk drugs	7
Patient with cisplatin (past 1/2 yr) and aminoglycoside	Contra-indication aminoglycoside; potentating nephrotoxicity	5
Patient with ganciclovir and platelets < 100 x 10^9/L, granulocytes < 30%, leucocytes < 4 X 10^9/L	Switch to foscavir	2
Patient with cotrimoxazole and platelets < 100 x 10^9/L, granulocytes < 30%, leucocytes < 4 X 10^9/L	Add folic acid or switch to alternative drug	2

Part III

Clinical validity

4

A computerized adverse drug event alerting system using clinical rules: A retrospective and prospective comparison with conventional medication surveillance in The Netherlands

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Abstract

Background: Adverse drug events (ADEs) are an important problem in hospital practice. Computerized physician order entry (CPOE) and clinical decision support systems (CDSS) are useful tools in the prevention of ADEs. In The Netherlands there are some basic CDSS within CPOE systems, but there is not much experience with sophisticated systems. We have recently developed a more advanced CDSS, a computerized adverse drug event alerting system (ADEAS).

Objective: The aim of the study was to compare the newly developed ADEAS, which uses a set of clinical rules, with the conventional medication surveillance, a basic CDSS within a CPOE, to assess its additional value in detecting patients with a potential ADE.

Setting: Leiden University Medical Center (LUMC), a university hospital in Leiden, The Netherlands.

Design: Two studies were carried out; one retrospective and one prospective. The retrospective comparison of ADEAS with conventional medication surveillance was conducted on all patients admitted to the hospital (except intensive care unit patients) during a 1-month period (15 November – 15 December 2006). A prospective comparison of both systems was performed during a 6-month period (May – October 2007) on one general internal medicine ward.

Measurements: The endpoint was the total number of alerts and content of alerts generated by both methods. In the prospective study we also focused on the number of unique alerts and interventions by the hospital pharmacist following the alerts.

Results: In the retrospective study, ADEAS generated 2010 alerts compared with 2322 generated by the conventional method. In the prospective study, 248 and 177 alerts were generated by ADEAS and the conventional method, respectively. The number of unique alerts was 85 (of which 72 were considered true positive alerts) and 136, respectively. The hospital pharmacist made 14 (19.4%) interventions following a true positive alert with ADEAS and 5 (3.7%) with the conventional method. The contents of alerts generated by ADEAS were different to the safety alerts generated by conventional medication surveillance. The conventional medication surveillance generated safety alerts regarding drug–drug interactions and drug-overdosing. ADEAS generated alerts regarding declined renal function or other laboratory abnormalities and absence of essential concurrent medication.

Conclusions: Compared with our conventional medication surveillance, the computerized alert system ADEAS selected different patients at risk of an ADE. This makes ADEAS in our hospital of additional value to the hospital pharmacist as a suitable tool in reducing the number of preventable ADEs.

Background

A substantial number of hospitalized patients experience harm due to medication. Different studies report that adverse drug events (ADEs) occur at a wide range of rates (0.17–65%) in hospitalized patients, and that approximately 50% are considered preventable [1]. In the literature, it is suggested that computerized physician order entry (CPOE) and clinical decision support systems (CDSS) can be important tools to facilitate the prevention of ADEs [2,3]. CPOE ensures complete, legible, standardized and clear orders, and CDSS are built into almost all CPOE systems to varying degrees. They can provide computerized advice, basic alerts regarding drug–drug interaction or more sophisticated alerts regarding drug-laboratory value checks. As far back as 1991, Classen et al. [4] described the development of a computerized system using algorithms or clinical rules to detect and characterize ADEs in hospital patients. In addition, Jha et al. [5] described that computer-based monitoring is an efficient way to identify ADEs compared with traditional detection methods. Later, such computerized alert systems were also used to prevent ADEs. Raschke et al. [6] developed a computer alert system to correct errors that might lead to ADEs and detect ADEs before maximum injury occurs. Also, Silverman et al. [7] used a computer-based system to prevent ADEs with clinical rules. They modified the rules used by Jha et al. [5] to include rules that identify actionable events and exclude rules that identify an ADE after it occurs (e.g. the ordering of an antidote) [7]. Meanwhile, different studies have shown that such CDSS within CPOE are successful strategies for reducing ADEs and medication errors [8-12].

In our hospital, the CPOE system in use provides online drug–drug interaction checks and drug-overdosing checks, but is not integrated with a sophisticated CDSS [13]. This current surveillance system has some limitations: 1) there is no possibility to adapt medication surveillance to categories of patients and/or to medical specialties; [14] 2) the system does not take into account relevant laboratory values; and 3) most alerts are of low clinical relevance, with the consequence of 'alert fatigue' [15]. Moreover, a recent Dutch study showed that implementation of such a CPOE with basic CDSS does reduce certain types of medication errors but not therapeutic errors and preventable ADEs [16]. Given these limitations, we decided to develop a new pharmacy decision support system that could improve the quality of our medication surveillance. The new system should both improve the specificity of the alerts compared with the current system and cover the lacking alerts, e.g. regarding declined renal function. As a result we have developed a computerized adverse drug event alerting system (ADEAS) with which patients at risk of an ADE can be detected electronically by combining more data available from the hospital information system and CPOE, using clinical rules [17]. We have already demonstrated that both the CPOE with

basic CDSS and clinical rules are useful early strategies for preventing medication-related harm [18].

In this study we report the results of a retrospective and prospective study in which the new ADEAS (a CDSS that uses a set of clinical rules) was compared with our conventional medication surveillance system (a basic CDSS within the CPOE) in order to assess its additional value in detecting patients with a potential ADE.

Methods

Setting

The two studies were performed in Leiden University Medical Center, a university hospital in Leiden, The Netherlands. Our hospital information system, Mirador® (iSOFT Nederland BV, Leiden, The Netherlands), includes integrated patient-specific data with demographics, laboratory results, discharge letters, medical diagnosis code, surgery reports, radiology reports and pharmacy orders. The existing CPOE system, Medicatie/EVS® (Medicator®; iSOFT Nederland BV), is incorporated within the hospital information system and is described in detail elsewhere [13]. Briefly, it provides online drug–drug interaction checks and drug-overdosing checks, but is not integrated with a sophisticated CDSS. The drug information on which the safety alerts are based is retrieved from a national drug information database, the 'G-standard' (Z-Index BV, The Hague, The Netherlands). The G-standard contains information about drugs available in The Netherlands, and the majority of Dutch pharmacy information systems use this database to support medication surveillance, prescribing, dispensing and logistics. Not all the features available in the G-standard are used within our CPOE with basic CDSS; only drug–drug interaction alerts and drug-overdosing alerts are generated.

Conventional medication surveillance method

The current procedure of our conventional medication surveillance is that hospital pharmacists perform daily retrospective checks of the drug–drug interaction and drug-overdosing alerts overridden by the physician. As described in the previous section, these are standard safety alerts from the national Dutch database (the G-standard) and are not fine-tuned to the local situation. In practice, most of the safety alerts are ignored by the physician while prescribing medication in the CPOE. All the ignored and overridden alerts

are collected in a Microsoft Access® database and the hospital pharmacist reviews these alerts the following day (except for the weekend, when the alerts are seen on Monday). If necessary, the hospital pharmacist checks laboratory values or co-medication, and selects potentially clinically relevant alerts to discuss with the prescribing physician.

New method: Adverse Drug Event Alerting System (ADEAS)

The new computerized alert system ADEAS uses clinical rules that describe potentially harmful drug-related situations based upon data from the hospital information system. The development of this expert system and the first set of clinical rules is described in detail elsewhere [17]. Briefly, ADEAS was composed in Gaston (Medecs BV, Eindhoven, The Netherlands), a guideline-based decision support framework consisting of both a guideline development module and a decision-support module. Selection of the potential patients at risk of an ADE occurs by combining data from the electronic patient file (EPF) [laboratory data, patient characteristics], the CPOE (prescribed medication) and the G-standard (drug data and drug–drug interaction data), using predefined algorithms, the so-called clinical rules. The guideline development module in Gaston is used to create and support the clinical rules. The decision support module is used to link Gaston with our hospital information system for the required information and to execute the clinical rules. The clinical rules were formulated in a multidisciplinary team using seven drug-related risk categories [17].

ADEAS processes the day's data throughout each night, determining potential patients at risk, and generates its output in the Pharmacy Department every morning. During both studies, approximately 121 clinical rules were used by the system [17].

Study design

Retrospective study

The retrospective study was performed during a 1-month period (15 November – 15 December 2006), in which ADEAS was compared with the conventional medication surveillance. For this study, all patients admitted to the hospital during this period, except intensive care unit (ICU) patients (because ICU uses a different EPF and CPOE), were included. During the study period the conventional medication surveillance method was performed daily as usual, as described above. ADEAS was also activated during the study period and the generated alerts were collected retrospectively at the end of the study. Consequently, no actions were taken following the alerts generated by ADEAS.

Prospective study

The prospective comparison between the two systems was performed during a 6-month period (May – October 2007). For this study, all patients admitted to one general internal medicine ward were included. Again, during the study period the conventional medication surveillance method was performed daily as usual, as described above. ADEAS was also activated during the study period, and everyday a hospital pharmacist evaluated the list of alerts generated by ADEAS to determine if the alert selected a potential clinically relevant situation that needed discussion with the prescribing physician (except for the weekend when the alerts were seen on Monday). Following alerts from both ADEAS and the conventional medications surveillance, the hospital pharmacist visited the ward or participated in the ward round to consult with the physician regarding the alert and, if necessary, gave additional advice.

Measurements

Retrospective study

The endpoints were the total number of alerts and the content of the alerts generated by the two systems.

Each day the total number of alerts, the number of patients with alerts and number of interventions by the hospital pharmacist were collected, as generated by the conventional medication surveillance method. At the end of the study period the daily total number of alerts and number of patients with alerts were collected, as generated by ADEAS.

The total number of alerts included duplicate alerts. Duplicate alerts can occur in the conventional medication surveillance; for example, when a physician prescribed then stopped and subsequently prescribed the same medication order again in a different dosage or different route, the accompanying alert is shown with each prescription. Duplicate alerts can also occur in ADEAS; for example, some clinical rules are built in a way that when the potential ADE situation continues to exist, an alert is generated every day.

Furthermore, we compared the content of the alerts (the detected potentially harmful situation regarding the patient) generated by the two systems. For ADEAS we selected the top five most frequently triggered clinical rules and determined if they were triggered by the conventional system as well.

Prospective study

The endpoints were the total number of alerts, the number of unique alerts, the content of the alerts generated by the two systems, the number of interventions by the hospital pharmacist and the number of accepted interventions.

Each day, the total number of alerts, the number of unique alerts, number of patients with alerts and number of interventions by the hospital pharmacist were collected, as generated by the two systems. Follow-up was checked for each intervention to measure the number of interventions accepted by the physician.

We determined if an alert in ADEAS was a true positive alert, i.e. a real potential ADE. Alerts in ADEAS can be false positive alerts because, for example, the rule is not specific enough (using classes of drugs instead of individual drugs). Another scenario is that drugs are prescribed by the physician as a free-text field order and not selected from the database within the CPOE. ADEAS cannot read free-text field items and can, in this way, miss prescribed drugs. Alternatively, a patient's disease, e.g. epilepsy, is identified via their specific medication for that disease, in this case antiepileptic drugs; however, in some cases the patients use the drugs for a different indication, e.g. neuropathic pain.

By reviewing the EPF of the patients, the hospital pharmacist determined if the alert was true positive or false positive. The percentage of interventions was calculated compared with the number of true positive alerts. The overall positive predictive value (PPV) for ADEAS was calculated by the quotient of the number of true positive alerts and the number of unique alerts.

Within ADEAS, for each separate clinical rule with a true positive alert we calculated the PPV for potential ADE and for intervention. The PPV per rule for potential ADE was calculated by the quotient of the number of patients with an alert considered an actual ADE and the total number of patients with an alert for that rule. The PPV per rule for intervention was calculated by the quotient of the number of interventions and the total number of patients with a true positive alert for that rule.

Results

Retrospective study

During the 31 days of the study period the mean number of patients present in the hospital was 352 per day (exclusive of ICU patients) [SD 49.1]. The conventional medication

monitoring system generated a total number of 2322 signals; on average 74.9 signals per day (SD 34.8). Results are presented in Table 4.1. Of the 2322 signals, 350 alerts resulted in an action by the pharmacist. Laboratory values of the patient were checked 255 times (mean 8.2 per day [SD 5.3]), but further intervention was not considered necessary, and 95 times (mean 3.1 per day [SD 3.6]) the pharmacist consulted the physician or nurse to propose an intervention. All the alerts generated by the conventional method were drug–drug interaction alerts and drug-overdosing alerts.

ADEAS generated a total of 2010 signals in the same period and in the same patient population; on average 64.8 signals per day (SD 22.3) [Table 4.1]. Of the 121 active rules, 53 different clinical rules were triggered at least once. The top five rules that were triggered most frequently are shown in Table 4.2. Of all these patients with potential harmful situations only some patients triggered by rule number 2 were also detected by the conventional method while the rest were not. The conventional system generated an alert in, for example, patients with the combination of an NSAID and an SSRI or corticosteroid. However, it generated this alert in all patients regardless of their age or concurrent medication, such as the use of pantoprazole. The alerts generated by ADEAS were related to laboratory value abnormalities, such as a declined renal function and concurrent use of drugs eliminated by the kidney, the absence of essential medication protecting the patient for an adverse drug reaction and other potentially harmful situations, e.g. a patient with a gastrointestinal tube. The data collection of the results with ADEAS was done retrospectively, therefore no interventions were made.

Prospective study

During the 6-month study period, measurements were performed on 139 consecutive days. The mean number of patients present at the general internal medicine ward was 5.6 per day (SD 3.1). Results are presented in Table 4.3.

Table 4.1 Results of the retrospective comparison of the Adverse Drug Event Alerting System (ADEAS) and conventional medication surveillance (CMS), hospital wide, during a 1-month period

Parameter	CMS	ADEAS
Total numbers of alerts	2322	2010
Average number of alerts per day (SD)	74.9 (34.8)	64.8 (22.3)
Average number of patients with an alert per day (SD)	41.4 (16.7)	54.6 (13.7)
Number of interventions	95	NA

NA, not applicable; SD, standard deviation.

Table 4.2 Retrospective study result of the Adverse Drug Event Alerting System (ADEAS); 'top five' most frequently triggered clinical rules during a 1-month study period

	Clinical rule	Total no. alerts	Total no. patients
1	Opioid receptor agonist prescribed more than 2 days ago, and no laxative added to the therapy to alleviate constipation	250	220
2	Patient > 70 years of age prescribed a NSAID (not COX-2 selective) and has no ulcer protection, or patient > 60 years of age prescribed NSAID (not COX-2 selective) with an additional risk factor for ulcer and has no PPI.	244	53
3	Patient with oral iron medication and addition prescription of a laxative for possible treatment of the adverse event constipation	198	26
4	Patient with a prescription for an oral drug given via the gastrointestinal tube	170	19
5	Patient with a creatinine clearance of less than 50 mL/min or a serum creatinine value > 150 µmol/L	137	56

COX, cyclooxygenase; PPI, proton pump inhibitor.

Table 4.3 Results of the prospective comparison of the Adverse Drug Event Alerting System (ADEAS) and conventional medication surveillance (CMS) on one general internal medicine ward during a 6-month period

Alerts and interventions	CMS	ADEAS
Total number of alerts	177	248
Number of unique alerts	136	85
Number of true positive alerts	136	72
Total number of patients with alert	57	48
Average number of alerts per day (SD)	1.3 (1.8)	1.8 (2.2)
Average number of patients with an alert per day (SD)	0.8 (0.9)	1.0 (1.1)
Number of interventions (%)	5 (3.7)	14 (19.4)
Number of interventions accepted by physician (%)	3 (60)	10 (71)

The total number of alerts with the conventional method was 177 and the number of unique alerts was 136. All 136 were true positive alerts. In five situations (3.7%) the pharmacist consulted the physician to propose an intervention, twice regarding a drug–drug interaction (lithium + diuretic and methadone + erythromycin) and three times concerning the dosages of a drug (possible incorrect dose of nitrofurantoin, cefuroxime and nadroparin regardless of renal function). Three times the proposed intervention was accepted by the physician.

Table 4.4 Prospective study result of the Adverse Drug Event Alerting System (ADEAS): the 20 different clinical rules responsible for the 72 true positive alerts

Clinical rule	No. patients with alert (A)	No. patients with real potential ADE [true positive] (B)	No. interventions (C)	PPV for real potential ADE [true positive] (B/A)	PPV for intervention (C/B)
Patient with CL_{CR} < 50 mL/min or plasma creatinine > 150 µmol/L	12	12	0[a]	1.00	0.00
Patient with therapeutic drug monitoring result of aminoglycoside or vancomycine therapy	8	8	2	1.00	0.25
Opioid receptor agonist prescribed more than 2 days ago, and no laxative added to the therapy to alleviate constipation	8	8	0[b]	1.00	0.00
Patient with plasma creatinine rise > 50% or > 50 µmol/L	10	7	1	0.70	0.14
Patient with low molecular weight heparin and CL_{CR} < 25 mL/min	4	3	1	0.75	0.33
Patient > 70 years of age prescribed a NSAID (not COX-2 selective) and has no ulcer protection, or patient > 60 years of age prescribed NSAID (not COX-2 selective) with an additional risk factor for ulcer and has no PPI	3	3	2	1.00	0.67
Patient (> 70 years) with digoxin (> 0.125 mg/day) or patient (> 70 years) with digoxin and CL_{CR} < 50 mL/min or creatinine rise > 50% or > 50 µmol/L	3	2	2	0.67	1.00
Patient with ciprofloxacin or norfloxacin and antiepileptic agents	2	2	0	1.00	0.00
Patient with biphosphonate and drug affecting absorption (iron, calcium, antacid)	3	2	0	0.67	0.00
Patient with iron (oral) and penicillamine, methyldopa, antacid or levodopa	1	1	0	1.00	0.00

Patient with cefuroxim and CL_{CR} < 50 mL/min.	3	1	1	0.33	1.00
Patient with ceftazidim and CL_{CR} < 100 mL/min.	4	1	1	0.25	1.00
Patient with ciprofloxacin and CL_{CR} < 25 mL/min	2	1	0	0.50	0.00
Patient with cotrimoxazole or dapson and no folic acid	2	1	1	0.50	1.00
Patient with ranitidine and CL_{CR} < 50 mL/min	1	1	0	1.00	0.00
Patient with acrivastine, levocetirizine or cetirizine and CL_{CR} < 10 mL/min	1	1	1	1.00	1.00
Patient with sulfonylurea agent and CL_{CR} < 10 mL/min or ALAT > 135 U/L or ASAT > 135 U/L	1	1	1	1.00	1.00
Patient with antipsychotic drug or antidepressant drug and ALAT > 135 U/L and ASAT > 135 U/L or bilirubine > 40 µmol/L	2	1	0	0.50	0.00
Patient receiving azathioprine[c]	1	1	0	1.00	0.00
Patient with gabapentin or pregabalin and CL_{CR} < 50 mL/min	1	1	1	1.00	1.00

a) Screening risk medication; if present and wrong dosages, then intervention
b) Mostly postsurgical "methadone if necessary"
c) Dosage check recommended by Dutch inspectorate authority; maximum daily dose 5 mg/kg.
ADE, adverse drug event; CL_{CR}, creatinine clearance; COX, cyclooxygenase; PPI, proton pump inhibitor; PPV, positive predictive value.

In the same period and in the same patient population, the total number of alerts generated by ADEAS was 248. The number of unique alerts was 85, of which 72 were considered true positive alerts, i.e. alerts regarding a real potential ADE. In 14 situations (19.4%) the pharmacist consulted the physician and gave additional advice. Ten times the intervention was accepted by the physician. The overall PPV for ADEAS was 0.85 (72/85).

Twenty different clinical rules were responsible for the 72 true positive alerts (Table 4.4). 'Creatinine clearance < 50 mL/min or plasma creatinine > 150 mmol/L' was the rule with the highest number of alerts (12 patients). For the 20 different clinical rules, the PPV for actual potential ADE varied between 0.25 and 1.00 (Table 4.4). The PPV for intervention varied between 0.00 and 1.00 (Table 4.4). For example, the rule regarding a declined renal function with the highest number of alerts never led to an intervention by the pharmacist. The pharmacist did screen the medication for dosage errors but none were found. Still, this rule detects a potential harmful situation, and was therefore considered a true positive alert with a high PPV for an actual potential ADE, but consequently a low PPV for intervention.

Discussion

With ADEAS, different kinds of patients at risk for an ADE were detected compared with the conventional medication surveillance. The number of alerts with ADEAS was lower than with the conventional surveillance method (both total number of alerts in the retrospective study and unique number of alerts in the prospective study), but the percentage of interventions by the hospital pharmacist with ADEAS was higher.

Safety alerts generated by the conventional medication surveillance in our CPOE consist of drug–drug interaction signals and drug-overdosing signals. As mentioned, these safety alerts are retrieved from the G-standard, a national database. They are not fine-tuned to the local situation or specialized to individual patients or medical specialties. ADEAS was developed to overcome these limitations so we could detect more, and in a more sensitive way, patients at risk of an ADE. The strength of ADEAS is that it uses more sources of information from the integrated databases available in the EPF, such as laboratory data, patient age and concurrent medication, to search for potentially harmful situations. Consequently, the alerts generated by ADEAS were related to laboratory value abnormalities, such as declined renal function, the absence of essential medication to protect the patient for an ADE, and the use of a gastrointestinal tube. In this way, ADEAS has, in our hospital, an additional value in detecting patients at risk of a potential ADE compared with conventional medication surveillance.

Our study shows that, in particular, clinical rules related to unadjusted drug dosages in patients with declined renal function are important triggers for potential ADEs, which is in line with the findings of other investigators [19-23]. The additional value of the new ADEAS system is also illustrated by the rule 'opioid receptor agonist and no prescription for laxative'. This rule gave a high number of alerts, both in the retrospective and prospective studies, whereas it did not generate alerts when using the conventional medication surveillance method.

Moreover, the added value of the new ADEAS system is also illustrated by a clinical rule regarding the prescription of an NSAID in a patient with a risk factor for ulcer-related bleeding and without a prescription for a proton pump inhibitor. The conventional system does generate an alert in, for example, a patient with the combination of an NSAID and an SSRI or corticosteroid. However, it gives an alert in all patients regardless of their age or concurrent medication, such as the use of pantoprazole. In the latter situation, the conventional system generates a false positive alert, which may lead to alert fatigue by the physician [15,24]. The system cannot 'read' the age of the patient or the concurrent medication, like ADEAS can. ADEAS only generates an alert when a proton pump inhibitor was absent and the patient was older than 70 years of age or older than 60 years of age with an additional risk factor.

Beside the content of the alerts, the number of alerts was also an endpoint in both studies. The total number of alerts included duplicate alerts. In an ideal system, duplicate signals are switched off or hidden when seen by the physician or pharmacist. Unfortunately, both our conventional system and the new ADEAS still show duplicate alerts. That is why we choose to compare the total number of alerts in the retrospective study. Although it gives less information, it is a reflection of our current practice. A limitation of ADEAS was that it generated more duplicate alerts than the conventional method. ADEAS has to become smarter in the future. In the prospective study we also focused on the number of unique alerts, which give more information about the capability of the system. Comparing the number of alerts between the prospective and retrospective studies is not desirable because the two studies are conducted on a different patient population. An official comparison of the two systems by means of PPV is not possible because the conventional system is a system designed to detect drug–drug interactions and drug-overdosing. It is not designed to be an ADE prediction system, as the new ADEAS is. This means we cannot calculate a PPV for the conventional method.

A limitation of the prospective study is that it was conducted on a small internal medicine ward. This also has consequences for the number of interventions and the proportion of accepted pharmacist interventions by the physician. They were higher with ADEAS than

with the conventional medication surveillance, but the absolute numbers were small (14 interventions, of which 10 were accepted, vs. 5 interventions, of which 3 were accepted).

Another limitation of our study is that we compared only two particular systems, and the systems are only used by a few hospitals in The Netherlands. This makes the generalizability of our results poor; however, as with most CPOE and CDSS, different commercial and locally designed applications are used worldwide. Comparability and generalizability of these investigations is usually poor, but the methods used in the different studies can be of help for other investigators.

Only a relatively small number of the clinical rules active in the system ADEAS resulted in alerts and the PPV for some rules was low. For example, the rule regarding a declined renal function with the highest number of alerts never led to an intervention by the pharmacist. The pharmacist did screen the medication for dosages errors but none were found. More specific rules, with a combination of a specific drug prescription and a declined renal function, had higher PPVs for intervention. Our set of clinical rules needs adaptation and modification in order to enlarge the amount of positive alerts. Adapting the content of the rules during use is an acceptable way to enlarge the PPV for the clinical rules [7]. In this way, with smarter clinical rules, the added value of ADEAS in detecting patients at risk can be greater. The overall PPV for ADEAS was good (0.85), but can be better. In the future we should investigate the possibility of combining the features of ADEAS with the G-standard and the conventional surveillance method to create a more sophisticated alerting system. Overall, ADEAS can be seen as a first step towards more advanced clinical decision support. The importance of preventing ADEs by using these types of alerts and computerized systems, such as ADEAS, is also stressed by others [6,25-28].

We believe that interaction between pharmacists and physicians will be increasingly appreciated when pharmacist interventions focus on specific patients at risk of developing ADEs. Studies have shown that participation of clinical pharmacists with the healthcare team on patient rounds indeed results in improved care [29]. ADEAS may be useful to create a more individualized patient-oriented pharmacy service on the hospital ward. By selecting at risk patients, and making goal-oriented visits to the ward, the pharmacist can be more time-efficient than by participating on ward rounds.

Conclusions

Compared with our conventional medication surveillance, the computerized alert system ADEAS selected different patients at risk of an ADE. This makes ADEAS in our hospital of added value to the hospital pharmacist as a suitable tool in reducing the number of preventable ADEs.

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Comparison of methods for identifying patients at risk of medication-related harm

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Abstract

Background: With the introduction of Computerised Physician Order Entry (CPOE) in routine hospital care, a great deal of effort has been but into refining Clinical Decision Support Systems (CDSS) to identify patients at risk of preventable medication-related harm.

Objectives: This study compared a CPOE with basic CDSS and 16 clinical rules with a manual pharmacist medication review to detect overdose and drug–drug interactions that actually required a change in medication.

Methods: The study involved the review of 313 patients admitted over five months at an internal medicine ward where a change in medication as a result of dosing of therapeutic errors was detected by a manual medication review by a trained pharmacist. Subsequently, all these patients' medication orders (MOs) were entered into the authors' CPOE with basic CDSS. Medication orders with a safety alert indicating overdose and drug–drug interactions generated by the authors' CPOE with basic CDSS were compared with the same type of medication errors identified through manual review. The positive predictive value (PPV), sensitivity and specificity compared with manual review were determined. Second, a set of 16 clinical rules was applied to the patient and prescribing data. The overlap between the clinical rules and manual review was determined by comparing patients triggered by the clinical rule with patients with a corresponding error in the manual medication review.

Results: Manual medication review identified 57 medication errors involving overdose and 143 therapeutic errors of which 46 were drug–drug interactions. The CPOE with basic CDSS generated 297 safety alerts involving overdose (PPV 0.06, sensitivity 0.32, specificity 0.92) and 365 safety alerts involving drug–drug interactions (PPV 0.12, sensitivity 0.96, specificity 0.91). The clinical rules generated 313 safety alerts identifying 39% of all the overdoses and therapeutic errors found in the manual review at which they were targeted. In 23% of the alerts generated by a clinical rule, the patients actually required a change of medication as indicated by the manual review. When CPOE with basic CDSS and the rules were combined, 66% of the overdoses and therapeutic errors were identified.

Conclusions: The authors' CPOE with basic CDSS and the clinical rules are useful early strategies for preventing medication-related harm. They could be a first step towards more advanced decision support. These computerised systems will be even more useful in daily practice, once they are further fine-tuned to decrease the number of alerts that need no clinical action.

Introduction

A substantial proportion of hospitalised patients experience medication-related harm that is preventable, for example due to incorrect dosing, contra-indicated drug choice or drug–drug interactions (DDIs) [1-4]. Strategies to prevent such problems are being developed. One such strategy is the structured review of patient medication (medication review) by physicians or pharmacists to identify patients with medication errors (MEs) that may lead to harm. In some settings, for example where clinical pharmacists do not routinely participate in ward rounds, this approach may have a retrospective character which implies late intervention, which may be too late to be effective. Moreover, this system is very labour-intensive, since all medication for all patients has to be systematically reviewed. The advantage is that the complete clinical status of each patient is taken into account when identifying problems. A less labour-intensive strategy is the use of computerised trigger systems. These systems can identify patients at risk of medication-related harm (adverse drug events, ADEs) using either data on the prescribed medication alone or the combination of medication with certain patient characteristics or clinical laboratory values [5-9]. An example of such a system is the Clinical Decision Support system (CDSS) within Computerised Physician Order Entry (CPOE) systems [10]. In The Netherlands, the CDSS integrated into most types of CPOE system is basic; only drug overdose and DDI alerts are generated. For successful identification of high-risk patients, more is required, such as identification of patients at risk of dosing problems in cases of clinical deviation from chemistry parameters or determined blood drug concentrations, or cases where a specific medicine for a specific disease needs to change [11,12]. Currently, some hospitals in The Netherlands are developing more advanced support in addition to their basic CDSS by creating defined clinical rules basically computerised algorithms that look for specific medication orders, patient characteristics and/or laboratory values that identify patients at risk of suboptimal therapy and of medication harm [13]. The advantage of such computerised system is that they limit labour input dramatically. Such systems should be sensitive enough to identify patients at risk, but also specific enough to generate clinically relevant alerts and thus prevent alert fatigue.

This study compared a CPOE with basic CDSS and 16 advanced clinical rules with a manual pharmacist medication review to detect overdose and DDIs that required a change in medication.

Methods

Setting and study population

This study was performed in two general internal medicine wards and one gastroenterology/rheumatology ward at the UMCG. All patients admitted for more than 24 h to these wards were included (313 patients). A waiver from the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of normal hospital routine for quality improvement. During the study period the system of medication ordering was a conventional paper-based system.

Study design and data collection

A trained research pharmacist (JEvD) visited the ward daily to collect the following data: patient characteristics, medical history, diseases, medication orders (MOs), and laboratory values. Data were extracted from the hospital information system, medical charts and administration charts.

Methods for identifying medication errors or patients at risk

Medication review method to identify medication errors

All MOs were reviewed by a trained research pharmacist (JEvD) with regard to the presence of medication errors (MEs) according to the classification scheme of The Netherlands Association of Hospital Pharmacists [14] and considering the complete clinical situation of the patient.

In this study, we included only dosing and therapeutic errors. These errors, if not corrected, have a high probability of leading to medication-related harm [2,15-18] and are therefore the prime target for CDSS.

CPOE with basic CDSS

All MOs were manually entered into a test environment in our CPOE with basic CDSS, the commercially available Medicator (iSOFT, Leiden, The Netherlands). The Medicator CDS(S) system is basic: safety alerts are generated only for overdoses or DDIs [19]. These safety alerts are shown to physicians during the prescribing phase when used in functioning systems. This medication surveillance is based on a national drug database for community pharmacies (the 'G-standard,' Z-index BV, The Hague, The Netherlands). After entering MOs

into the system, all safety alerts generated were collected, and both MOs and safety alerts (overdose or DDI) were recorded in an SPSS data- base (version 14; SPSS, Chicago, Illinois).

Computer based clinical rules

Leiden University Medical Center (LUMC) has developed a computerised alert system that uses clinical rules to detect patients with a potential ADE or who are at risk of an ADE. The system uses data combined from the CPOE, the hospital information system (e.g., laboratory values) and the national drug information database ('G-Standard') to detect potential patients at risk. Detection is based on defined algorithms, so-called clinical rules. Currently, more than 100 clinical rules have been defined and agreed on by a multidisciplinary team including a pharmacist, a hospital pharmacist, an internal medicine specialist and a clinical pharmacologist. The clinical rules and the computer system have been tested and validated [20]. A 5-month pilot study at a general internal medicine ward was performed in the LUMC to compare this new computerised alert system with conventional medication surveillance in their CPOE/CDSS to assess its additional value. Twenty different clinical rules led to an alert in the small patient population admitted to this ward [21].

In the current study, which compared this computerised approach with the patients identified as having medication errors, we excluded four rules that were not defined as medication errors in the medication review, resulting in a set of 16 rules (see Table 5.5). A query was designed in MS Access 2003 (Microsoft, Seattle, Washington) for each clinical rule. These queries were applied to the patient data to assess how many patients were triggered by the clinical rules.

Analysis

SPSS version 14 was used for the analysis. Safety alerts generated by CPOE with basic CDSS were compared with overdose or DDI errors detected by the medication review method for all the MOs. The overlap between CDSS and medication review method was analysed by calculating sensitivity, specificity and positive predictive value (PPV) of the support on overdoses and the support on DDIs. The overlap between clinical rules and medication review method was analysed for those patients identified by the clinical rules as being at risk, and limited to patients with an identical medication error. Sensitivity and specificity were not calculated, since patients without an alert and with a related medication error were not included. The overlap was manually reviewed and subsequently analysed by calculating the percentage of patients who were identified as being at risk by both systems. Those

patients with an error that corresponded to the related clinical rule were identified only by the medication review method.

Results

The 313 patients making up our study population covered a wide age range of adult patients with diverse clinical conditions, as expected on a general medicine ward. They ranged from young adults with Crohn's disease to the frail elderly with polypharmacy (Table 5.1). Using the medication review method, 622 dosing errors and 143 therapeutic errors were found. The different types of dosing and therapeutic errors are shown in Table 5.2. The 'overdose' and 'DDI' subtypes were detected 57 and 46 times respectively.

Table 5.1 Study population

Parameter	
Age (mean ± SD)	58.1 ± 19.4
Female (%)	58.5
Medication orders per hospital stay (mean ± SD)	11.4 ± 7.9
Patients internal medicine (n)	125
Patients gastroenterology/rheumatology (n)	188
Total patients	313

Table 5.2 Frequency of different types of errors: medication review method

Type of medication error	No
Dosing	
Strength	205
Dosing frequency	199
Overdose	57
No maximum for "as needed"	99
Underdose	35
Duration of therapy	17
Directions of use	10
Total	622
Therapeutic	
Indication	19
Contraindication	19
Drug–drug interaction	46
Improper monotherapy	18
(Pseudo)double medication	40
Therapeutic monitoring	1
Total	143

In total, 297 overdose safety alerts were generated by our CPOE with basic CDSS. The PPV of this type of support was low (0.06), that is few of the generated safety alerts were indeed indicated as actual overdoses by the medication review method. The sensitivity of the support was higher but still not optimal (0.32) (Table 5.3).

In total, 365 safety alerts on DDI safety alerts were generated by the CPOE with basic CDSS. Although the PPV was low (0.12), the sensitivity of the support was high (0.96; Table 5.4). Almost all DDIs resulted in an alert by the system, but the majority of the problems were not considered as medication errors by the medication review method when other patient data were taken into account.

The set of 16 clinical rules generated a total of 313 alerts, 72 (23%) of which also had one or more related ME identified by the medication review method. These were 78 MEs in total (data not shown). Accordingly, 23% of the alerts identifying patients at risk of medication-related harm actually required follow-up change in medication or some other action to

Table 5.3 Computerised physician order entry with basic clinical decision support systems: support on overdose

		Overdose by medication review (reference)		
		Yes	No	Medication orders (n)
Overdose safety alerts	Yes	18	279	297
	No	39	3224	3263
Total		57	3503	3560

Sensitivity = 0.32
Specificity = 0.92
Positive predictive value = 0.06

Table 5.4 Computerised physician order entry with basic clinical decision support systems: support on drug–drug interactions

		Drug–drug interactions in medication review (reference)		
		Yes	No	Medication orders (n)
Safety alerts on drug–drug interactions	Yes	44	321	365
	No	2	3193	3195
Total		46	3514	3560

Sensitivity = 0.96
Specificity = 0.91
Positive predictive value = 0.12

prevent an ME. The percentage of patients actually requiring a change in medication for two rules could not be determined because no patients were appropriately triggered, and this percentage was zero for seven clinical rules. For the other clinical rules, this percentage varied between 10 and 58% (Table 5.5). The percentage was highest for the rule 'use of an opioid and no prescription for a laxative' (58%). The main focus of the rest of the clinical rules set was to prevent potential therapeutic errors and potential overdoses with relation to reduced renal function. The medication review method found 143 therapeutic errors and

Table 5.5 Selected set of 16 clinical rules

Clinical rule	No of safety alerts: that is patients triggered by clinical rule	No of patients with a corresponding error in medication review (%)
1. Clearance < 50 ml/min or serum creatinine > 150 mmol/l	129	23 (18)
2. Serum creatinine increase of > 50 mmol/l or of > 50%	37	11 (30)
3. Use of cefuroxime and clearance < 50 ml/min	7	0 (0)
4. Use of ceftazidime and clearance of < 100 ml/min	2	0 (0)
5. Use of ciprofloxacin and clearance of < 25 ml/min	11	2 (18)
6. Use of ranitidine and clearance of < 50 ml/min	5	1 (20)
7. Use of cetirizine and clearance of < 10 ml/min	0	0 (e)
8. Use of sulfonamides urea derivate and clearance of < 10 ml/min	0	0 (e)
9. Gabapentine of pregabaline and clearance of < 50 ml/min	1	0 (0)
10. Use of digoxin > 0.0625 mg once daily and age > 70 years or clearance < 50 ml/min or low level of K or unknown level of K	14	0 (0)
11. A serum level of an aminoglycoside or vancomycin	3	0 (0)
12. Use of opioid and no prescription for laxative	45	26 (58)
13. Use of ciprofloxacin or norfloxacin and use of antiepileptic	2	0 (0)
14. Use of bisphosphonate and a drug which has an effect on absorption	29	3 (10)
15. Use of iron and a drug which forms a complex with iron	11	6 (55)
16. Use of azathioprine (check dose)	17	0 (0)
Total	313	72 (23)

57 overdoses (Table 5.2). The set of 16 clinical rules thus identified 78 MEs that is 39% of the 143 therapeutic errors and 57 overdoses identified by the medication review. Together, our CPOE with basic CDSS and the clinical rules detected 18 overdoses + 44 DDIs + 69 clinical rule alerts (excluding rule 14, which triggered patients who had already been detected by basic CDSS) = 131 (66%) of the 200 overdose and prescribing errors found using the medication review method.

Table 5.6 provides some examples of why patients found to be at risk of medication harm by the basic CDSS within the CPOE or the clinical rules were not considered to have medication errors to the medication review method.

Table 5.6 Signal with computerized physician order entry/clinical decision support systems (CPOE/CDSS) or clinical rule but no medication error in medication review

Signal	Reasoning
CPOE/CDSS overdose for example: Furosemide intravenous 40 mg once daily Amoxicillin intravenous 1 g four times daily Omeprazole intravenous 40 mg twice daily	All these doses are well accepted in a clinical setting in a more severely ill patient population and deviate from the maximum recommended doses in a community setting for which the medication control database was developed
CPOE/CDSS drug–drug interaction for example: non-steroid anti-inflammatory drugs and prednisolone	Due to the increased risk of gastrointestinal irritation this combination should be avoided or gastric protection should be provided. Where a proton pump inhibitor was administered simultaneously, this interaction was not considered a medication error, as the appropriate action had been taken.
Clinical rules for example number: 12. Use of opioid and no prescription for laxative 10. Digoxin rule (Table 5.5) 1. to 10. impaired renal function and potential for drug overdose	12. Patient receives only a single dose of opiate (e.g., morphine intravenous start) or has diarrhea when the signal is generated 10. For example patient has low potassium levels but gets potassium suppletion 1. to 10. Dose has been adapted in line with recommendations of the level of renal impairment

Discussion

A considerable number of patients identified as at risk of medication-related harm by the two computerised systems, the CPOE with basic CDSS and the clinical rules, were found not to be so using the medication review method. Nevertheless, the sensitivity and specificity of the CPOE with basic CDSS in signalling DDIs were good, despite the low PPV. This study

also shows that with a small set of clinical rules, a fair proportion (39%) of the medication errors detected by medication review can be prevented, and when the two systems are combined, this result increases to 66%.

CPOE/CDSS

In their review of medication-related clinical decision support in CPOE systems, Kuperman et al. [22] showed that CDSS can be divided into two stages: basic support, which covers the basic principles of support such as DDI checking and basic dosing guidance; and more advanced support, which also covers more complex support such as dosing support for susceptible patients or guidance for medication-related laboratory testing. The Medicator CDSS can be considered as basic. Our set of clinical rules are a first step towards more advanced clinical decision support combining basic CDSS (e.g., DDIs) and advanced CDSS (e.g., providing dosing support for patients with renal insufficiency). Because both our CPOE with basic CDSS and the clinical rules set focus only on a part of the spectrum of medication-related problems, they should be developed further to cover more potential problems. However, it is first important to ensure that the current support is optimised.

Our findings show that this CPOE with a basic CDSS package generates far fewer relevant signals (PPV ≤ 0.12) reporting overdoses or DDIs which do not actually need a subsequent change in medication. Nevertheless, CPOE with basic CDSS missed a considerable number of overdoses (sensitivity = 0.32) identified through medication review. One reason for this low sensitivity may be the lack of dosing support for susceptible patients (patients with renal failure or geriatric patients), one of the features of more advanced support systems such as the clinical rules. The low PPV could be explained by the fact that the alerts are based on a database designed for community pharmacies (the 'G-standard') rather than for hospital pharmacies. This leads to a number of irrelevant alerts for the hospital setting, such as overdose alerts for doses, which are perfectly acceptable in hospital but not in ambulatory care. To increase the PPV, this database should be further adapted to the hospital setting to prevent alert fatigue in hospital physicians [23].

Despite the high sensitivity and specificity of the DDI alerts, many alerts were generated that did not need a subsequent change in medication (low PPV). The challenge is thus to strike an optimal balance between the number of alerts that do not need a follow-up and preserving sufficient sensitivity to catch serious DDIs or overdoses. The most relevant determinant for including an alert should be the severity of the consequences of the overdose or DDI [24]. These considerations have led to the development of the clinical rules discussed below.

Clinical rules

In this study, we tested a small set of clinical rules. Overall, the clinical rules meant an improvement in identifying patients at risk and needing an actual change in medication. Whereas only up to 12% of the alerts generated by our CPOE with basic CDSS required a subsequent change in medication, this was 23% of the alerts generated by the clinical rules. When the two were combined, two-thirds of the medication errors were identified.

Like the basic CDSS, some of the signals generated by the clinical rules did not require a subsequent change in medication. For example, rules 1-9 on the use of medication and reduced renal function (Table 5.5) could be made more efficient by incorporating a cut-off dose below which no action and thus no alert are required. Other trigger tools have been developed with the same intention [5-7,9,25-27]. Some of these studies compared their tools with other methods to identify medication errors and ADEs such as manual review or voluntary reports [6,7]. Others only verified the signals generated on the presence of medication errors or ADEs [5,9,25]. Although these studies are positive in their conclusions, they all showed that additional information usually needs to be collected about the individual patient before the actual need to change medication can be known.

Our study was limited by the fact that the medication review method was performed by only one investigator. However, a strict classification scheme was used to identify medication errors. This scheme precisely distinguished different between subtypes of medication errors and did not allow much room for differences in interpretation. The investigator was extensively trained in using this classification scheme. Another limitation of this study was that the set of clinical rules studied was small (only 16 rules). The majority of these rules focused on support for patients with renal failure and thus covered a narrow therapeutic area. Other studies have assessed more diverse rules, which provide further information about the effect of computerised rules in the field of different therapeutic areas [6,26,28].

Conclusions

We conclude that our CPOE with basic CDSS and the clinical rules are useful early strategies to prevent medication-related a harm. They could be a first step towards more advanced decision support. These computerised systems will be even more useful in daily practice when they are further fine-tuned to decrease the number of alerts that require no clinical action. Currently, however, computerised systems should still be combined with a manual review approach to guarantee medication safety.

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Part IV

Clinical utility

6

Preventing adverse drug events in the elderly patient with polypharmacy by use of clinical rules and interventions by hospital pharmacists

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Abstract

Introduction: The computerized tool Adverse Drug Event Alerting System (ADEAS) is a clinical decision support system for the pharmacy and is developed as a method for performing more sophisticated medication surveillance. ADEAS applies clinical rules and can be used to select patients at risk of an adverse drug event (ADE).

Objective: This study investigates the extent in which ADEAS based interventions by hospital pharmacists prevent ADEs.

Setting: Leiden University Medical Center (LUMC) on five different internal medicine and cardiology wards.

Design: Frequencies of ADEs were estimated at baseline period and during a period after implementation of ADEAS (intervention period). ADEs were identified by chart review using a trigger list. Patients 65 years of age or older and using five or more different medications at admission were included. During the baseline period only conventional medication surveillance was performed. During the intervention period conventional medication surveillance and ADEAS were used. Hospital pharmacist made preventive interventions based upon alerts generated by ADEAS.

Measurement: Primary endpoint was the number of preventable ADEs compared in both study periods.

Results: In the baseline period, 223 patients were included during 240 admissions. In the intervention period 236 patients were included during 248 admissions. In the baseline period 42 preventable ADEs (0.18 preventable ADEs per admission) were found compared to 27 ADEs (0.11 preventable ADEs per admission) in the intervention period ($P < 0.01$, Chi square test).

Conclusion: Use of ADEAS and subsequent interventions by the hospital pharmacists showed a significant reduction of preventable ADEs in our hospital.

Introduction

Patient safety remains an important issue and consequently preventing patient harm in health care settings is crucial. Prescribing drugs to cure patients or to relieve symptoms represent the most common medical intervention but Adverse Drug Events (ADE) also attribute considerably to patient harm. Different methods to prevent ADEs are described in the literature, such as barcode scanning of drugs and patients, clinical pharmacist interventions on ward rounds, use of computerized physician order entry (CPOE) with or without clinical decision support systems (CDSS) and the use of robots for drug dispensing [1]. It is suggested that computerized tools, such as CDSS, are one of the important tools to prevent ADEs [1-3]. With this aim we have developed the computerized tool Adverse Drug Event Alerting System (ADEAS) for selecting patients at risk of an ADE [4]. ADEAS is a clinical decision support system for the pharmacy and is meant as a sophisticated medication surveillance system. It applies clinical rules combining information from multiple electronic sources. ADEAS is more sophisticated than our conventional medication surveillance because it selects through the use of algorithms, the so-called clinical rules, the patients at risk of an ADE. In this way the hospital pharmacist can pay attention to the medication of that patient who needs it the most and make preventive interventions. The development of this expert system including the first set of clinical rules is described in detail elsewhere [4]. Briefly, ADEAS was composed in Gaston (Medecs BV, Eindhoven, The Netherlands), a guideline-based decision support framework, consisting of both a guideline development module and a decision support module. Selection of the potential patients at risk of an ADE occurs by combining data from the electronic patient file (EPF) (laboratory data, patient characteristics), the CPOE (prescribed medication) and the 'G-standard' (National drug data and drug-drug interaction database). The guideline development module in Gaston is used to create and support the clinical rules. The decision support module is used to link Gaston with our hospital information system for the required patient related information and to execute the clinical rules. The clinical rules were formulated in a multidisciplinary team using seven drug related risk categories [4].

In a previous study we compared ADEAS with our conventional medication surveillance procedures and showed that ADEAS has an additional value specifically in selecting patients at risk of an ADE and lead to more interventions by the hospital pharmacist [5]. The aim of the current study is to investigate the extent in which ADEAS based interventions by the hospital pharmacist actually prevent ADEs in elderly patients with polypharmacy in the clinical setting.

Methods

Setting and patients

The study was performed in Leiden University Medical Center (LUMC), a university hospital in Leiden, The Netherlands. The study was conducted on five wards: haematology, cardiology, combined lung/gastrointestinal diseases ward, and two combined internal medicine wards covering the specialism's endocrinology, nephrology, infectious diseases, oncology, rheumatology and general internal medicine. Patients admitted to the five wards were included in the current study if they were 65 years of age or older and had five or more different medications at admission (polypharmacy). Exclusion criteria were admission less than 24 hours, scheduled admission for chemotherapy or Internal Cardiac Device (ICD) implantation. The study included 2 time spans: a 4-month baseline period, and a 3-month intervention period (see Figure 6.1). The length of the period was determined by the time it lasted until 250 consecutive patients were included in each period. During the baseline and intervention period the ADE measurements were performed. The hospital pharmacist made ADEAS-based intervention during the intervention period, and not during the baseline period. The period between the baseline and intervention period, the run-in period, was needed to get used to the ADEAS system and to update the system. During the entire study period all patients received standard pharmaceutical care which included conventional medication surveillance as described below.

The research protocol was submitted for consideration to the Medical Ethics Committee of the LUMC before start of the study. This Committee judged the protocol as not needing medical ethical approval. All data were collected anonymously.

Baseline period	Implementation period (Run-in period)	Intervention period
Standard pharmaceutical care	Standard pharmaceutical care	Standard pharmaceutical care
	Testing and introduction of ADEAS	Routine ADEAS + interventions hospital pharmacist
Baseline measurement: ADE collection by chart review		*Intervention measurement: ADE collection by chart review*

Figure 6.1 Outline study.

Standard pharmaceutical care

During the entire study period standard pharmaceutical care was given to all admitted patients in the hospital including those participating in this study. Standard pharmaceutical care is the same as our conventional medication surveillance and consists of daily retrospective checks by the hospital pharmacist of the drug-drug interaction and drug-overdosing alerts overridden during electronic prescribing by the physician. All the ignored and overridden alerts are collected in a Microsoft Access® database in the central pharmacy and the hospital pharmacists review these alerts the following day (except for the weekend, when the alerts are seen on Monday). If necessary, the hospital pharmacist checks laboratory values or co-medication, and selects potentially clinically relevant alerts to discuss with the prescribing physician. In addition, advices are given following therapeutic drug monitoring results. Our hospital information system, Mirador® (iSOFT Nederland BV, Leiden, The Netherlands), includes integrated patient-specific data with demographics, laboratory results, discharge letters, medical diagnosis code, surgery reports, radiology reports and pharmacy orders. The CPOE system, Medicatie/EVS® (Medicator®) (iSOFT Nederland BV, Leiden, The Netherlands), is incorporated in Mirador and is described in detail elsewhere [6]. Briefly, Medicator provides online drug-drug interaction checks and drug-overdosing checks, but is not integrated with a sophisticated CDSS. The drug information on which the safety alerts are based is retrieved from a national drug information database the 'G-standard' (Z-Index BV, The Hague, The Netherlands). The 'G-standard' contains information about drugs available in The Netherlands and the majority of Dutch pharmacy information systems use this database to support medication surveillance, prescribing, dispensing, and pharmacy logistics.

Study design

The study is a prospective, non-randomized intervention study. During baseline and intervention period chart review was used to collect the number of ADEs during admission. An independent research pharmacist (YH for baseline period and MBJ for intervention period) manually reviewed the paper and electronic chart of all included patients using a paper trigger list. This list consists of clinical symptoms and laboratory abnormalities which may be an indicator of the presence of a drug-related ADE. This list was composed using information from the Dutch POEMS study, Dutch HARM investigation, the national drug information database the 'G-standard' and other literature references [7-9]. With this list ADEs were searched in the chart and if possible linked to the drug use by the patient.

For both baseline and intervention period all charts were evaluated independently by a second reviewer, an internal medicine specialist (HA) and all ADEs found by the research pharmacist were discussed. All ADEs were classified by the two reviewers (research pharmacist and internal medicine specialist) to the following criteria: causality, severity and preventability. Causality assessment was done using a simplified Yale algorithm, also used in the Dutch POEMS study [10]. Severity scaling was done using the Common Terminology Criteria for Adverse Events (CTCAE) system [11]. Preventability was independently judged by the clinical knowledge of the two reviewers. ADEs are considered preventable if they were due to an error. When there were disagreements that affected classification of an event, the two reviewers met and reached consensus. If consensus could not be reached, a third reviewer, a hospital pharmacist (MR or IT), evaluated the event.

ADEAS based interventions

ADEAS was introduced on the five study wards during a run-in period while no changes were made regarding performance of standard pharmaceutical care (see Figure 6.1). ADEAS was run every night selecting potential patients at risk based upon the clinical rules and output was generated in the pharmacy department every morning. In the weekends, the retrieved patients and alerts were collected on Monday. During run-in and intervention period 121 clinical rules were implemented into the system [5]. Additional case specific information was subsequently collected for each patient by the hospital pharmacist and used to assess the clinical relevance of the alert for the specific patient. Consequently, if necessary, interventions were made by the hospital pharmacist following alerts from ADEAS. ADEAS alerts were categorized as follows:

1. the alert needed no intervention because the alert was false positive or the alert was considered not clinically relevant for this specific patient (for example after dose check or laboratory control);
2. the hospital pharmacist consulted the physician or nurse (by phone or by ward visit) to discuss the alert, for clarification, which did not result in an advice to alter therapy or treatment;
3. the hospital pharmacist consulted the physician or nurse and they agreed that the patient was at risk of a possible ADE. This resulted in an advice aimed to prevent the possible ADE.

For the intervention period, the total number of alerts following ADEAS, the number of patients with an alert and the number of alerts in each category was calculated. Following alerts with advice the percentage of acceptance by the healthcare professional was scored.

Measurements

The primary endpoint was the number of preventable ADEs found in the baseline period compared to the number of preventable ADEs in the intervention period. As secondary endpoints the total number of ADEs (including causality and severity assessment), the number of alerts generated by ADEAS and number interventions by the hospital pharmacist were evaluated.

Statistics

Comparison of number of preventable ADEs between baseline and intervention group was made using chi-square test with 1 degree of freedom (df).

We expected an average of 15 preventable ADEs per 100 admissions, based upon results of the Dutch POEMS study [9,12]. Approximately 50% of ADEs in hospitalized patients were assumed to be preventable [13]. To detect a 50% reduction in ADEs (80% power at a 0.05 significance level) a sample size of 496 admissions equally distributed over baseline and intervention periods was needed.

Results

In the baseline period, 223 patients were included during 240 admissions (10 patients were excluded because retrospectively they did not meet the inclusion criteria). Sixteen patients were admitted twice and one patient was admitted three times during the baseline period. In the intervention period, 236 patients were included during 248 admissions (2 patients were excluded because retrospectively they did not meet the inclusion criteria). Thirteen patients were admitted twice during the intervention period. The patient characteristics are shown in Table 6.1. All patients were 65 years of age or older and had five or more different drugs at admission and stayed in the hospital more than 24 hours.

Table 6.2 shows the primary endpoint, number of preventable ADEs per admission. A total of 88 ADEs were collected in the baseline period in 70 out of 240 admissions (mean 0.37 per admission), compared to 97 ADEs in the intervention period in 70 out of 248 admissions (mean 0.39 per admission). In the baseline period 42 preventable ADEs (0.18 preventable ADEs per admission) were found compared to 27 ADEs (0.11 preventable ADEs per admission) in the intervention period ($P < 0.01$, Chi square test 1 df); a significant difference. Examples of preventable ADEs are constipation due to codeine and other opioids, worsening

Table 6.1 Patients' characteristics

	Baseline period	Intervention period
Included patient admissions	240	248
Included number of different patients	223	236
Age	73.5 (SD 6.7)	72.9 (SD 6.0)
Sex (M)	150/240 (67%)	160/248 (65%)
Medium length of stay (day)	6.2 (SD 6.4, range 1–48)	5.9 (SD 6.4, range 1–38)
Division specialism – admissions		
Cardiology	133	143
Lung	40	27
Gastrointestinal	12	4
Haematology	8	10
General internal medicine*	--	21
Endocrinology	13	4
Nephrology	9	29
Rheumatology	6	2
Oncology	4	1
Infectious diseases	15	7

* Not included during baseline due to another pilot study.

Table 6.2 Primary endpoint: number of preventable ADEs

ADEs	Baseline period (N = 240 admissions)	Intervention period (N = 248 admissions)	P-value*
Not preventable	46 (0.19/admission)	70 (0.28/admission)	
Preventable (possible and definitely)	42 (0.18/admission)	27 (0.11/admission)	P < 0.01
Total	88 (0.37/admission)	97 (0.39/admission)	

* Chi square test with 1 df.

of Parkinson disease symptoms due to start promethazine, hypokalemia during diuretic use and orthostatic hypotension due to levodopa-carbidopa overdosing.

Table 6.3 shows the number of ADEs divided per specialism. The causality, severity and preventability assessment of the ADEs are shown in Table 6.4.

Results interventions ADEAS

During the intervention period ADEAS generated in total 521 alerts. Most alerts (474, 91%) needed no intervention; after dose check or lab control the alerts were considered not clinically relevant for the specific patient (category 1). In 47 (9%) alerts (in 33 different

Table 6.3 Number of ADEs found with chart review per specialism

Specialism's wards	Baseline period: ADEs = 88 (0.37/admission)	Intervention period: ADEs = 97 (0.39/admission)
Cardiology	36 (0.27/adm; 41%)	26 (0.18/adm; 27%)
Lung	19 (0.48/adm; 22%)	20 (0.74/adm; 21%)
Gastrointestinal	5 (0.42/adm; 6%)	4 (1.00/adm; 4%)
Hematology	3 (0.38/adm; 3%)	6 (0.60/adm; 6%)
General internal medicine*	--	12 (0.57/adm; 12%)
Endocrinology	3 (0.23/adm; 3%)	0
Nephrology	8 (0.89/adm; 9%)	27 (0.93/adm; 28%)
Rheumatology	3 (0.50/adm; 3%)	0
Oncology	0	0
Infectious diseases	11 (0.73/adm; 13%)	2 (0.28/adm; 2%)

* Not included during baseline due to another pilot study.

Table 6.4 Causality, severity and preventability assessment of ADEs

ADE criteria	Baseline period (N = 88)	Intervention period (N = 97)
Causality		
≥ -3 and < 0 (unlikely)	0 (0%)	0 (0%)
≥ 0 and ≤ +3 (possible)	15 (17%)	25 (26%)
+ 4 (probable)	73 (83%)	72 (74%)
Severity		
1 – mild	13 (15%)	24 (25%)
2 – moderate	46 (52%)	41 (42%)
3 – severe	24 (27%)	20 (21%)
4 – life-treating or disabling	5 (6%)	11 (11%)
5 – death related	0 (0%)	1 (1%)
Preventability		
Not preventable	46 (52%)	70 (72%)
Possible preventable	18 (21%)	5 (5%)
Definitely preventable	24 (27%)	22 (23%)

patients) the hospital pharmacist consulted the physician (category 2 & 3). In 39 out of 47 consults the pharmacist gave additional advice to prevent the possible ADE (category 3). Sixteen advices were accepted by the nurse or physician (41%) and the remaining 23 advices were not accepted or it was unknown if they were accepted. The flowchart of the results with ADEAS is shown in Figure 6.2. The different types of advice given by the hospital pharmacist are shown in Table 6.5.

Table 6.5 Types of advices following alerts from ADEAS during intervention period

Type of advice	Number of alerts with advice
Dose adjustment	16
Stop medication	1
Change medication	4
Monitoring side effects	2
Take drugs separately	8
Add medication	8
Therapeutic drug monitoring	2
Total	41*

* 2 patients had two advices: dose adjustment or stop medication and dose adjustment and monitoring side effects.

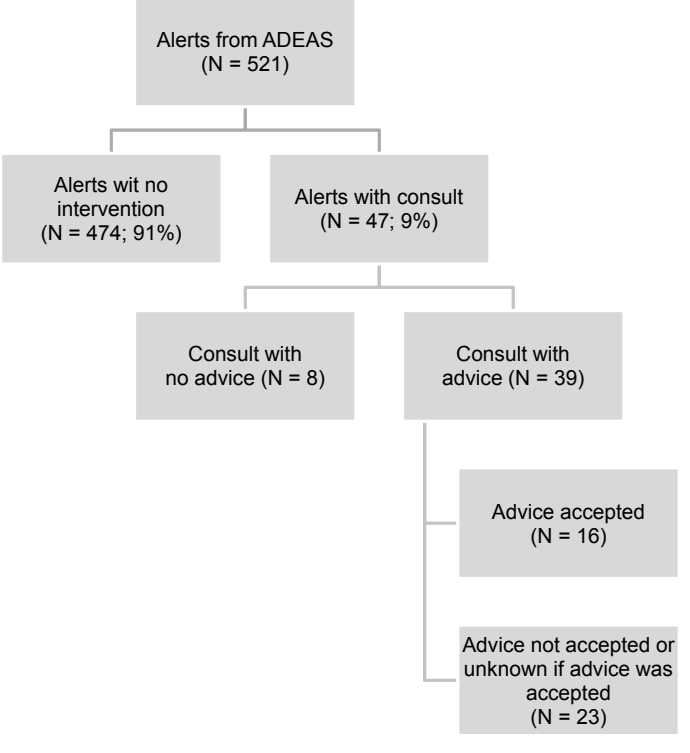

Figure 6.2 Results alerts with ADEAS during intervention period.

Discussion

This study shows that the ADEAS based interventions by the hospital pharmacist were effective in reducing the number of possible and definitely preventable ADEs. The number of preventable ADEs was significantly lower in the intervention period compared to the baseline period. However, the total number of ADEs before and after implementation of ADEAS remained constant.

The finding that the number of preventable ADEs is lower in the intervention period, is in line with our expectations. In the intervention period ADEAS was used, and ADEAS is designed to select patients with a potential ADE. Alerts generated by ADEAS lead to an action by the hospital pharmacist regarding the patient at risk, which could have prevented the ADE. Potential ADEs, in contrast to actual ADEs, are medication errors with the potential to cause injury but which do not necessarily cause any injury [8,14]. Medication errors, or extrinsic harm, are related to the manner the drugs used and can be prevented by interventions more easily. In particular, ADEs due to error or negligence are preventable [15]. Indeed, the alert system ADEAS contains clinical rules that search for these situations, such as medication dosages not adapted to a declined renal function, an opioid agonist prescribed without a laxative or a drug-drug interaction between cyclosporine and voriconazol without therapeutic drug monitoring.

In contrast to the number of preventable ADEs, the total number of ADEs was equal in the baseline and intervention period, caused by a higher number of non-preventable ADEs in the intervention period. Non preventable ADEs, also referred to as intrinsic harm or adverse drug reactions, are the result of the pharmacological properties of the drug itself [3]. An explanation for this can be the non-equal distribution of specialisms between baseline and intervention period. The inclusion of all consecutively admitted patients who met the inclusion criteria resulted in this non equal distribution of specialisms. In the intervention period more patients were admitted at the nephrology and general internal medicine department. The fact that more patients were admitted at the nephrology department in the intervention period could have had an influence on the relatively large proportion non-preventable ADEs in the intervention period. Indeed in the intervention period 27 ADEs were found in patients admitted to the nephrology department compared to 8 in the baseline period. At the nephrology department mostly kidney transplant patient are admitted which use immunosuppressive medication causing frequently adverse drug reactions which are by definition unpreventable. For example in the intervention period 8 non-preventable ADEs were found regarding hyperglycaemia and deregulation of diabetes mellitus due to

prednisolon. The median length of stay and the study population, the elderly patient with polypharmacy, was equal in baseline and intervention period.

The number of ADEs per admission in the baseline period and the percentage considered preventable in our study is comparable with ADE rates found in the literature [13]. The Dutch POEMS study found 15 preventable ADEs per 100 admissions [9,12]. We found a comparable number of 17.5 possible or definitely preventable ADEs per 100 admissions in the baseline period. Due to our ADEAS based interventions this number declined to 11 possible or definitely preventable ADEs per 100 admissions, a 37% reduction.

This study does not allow to indirectly compare ADEAS to the effects of other interventions aimed at reducing medication errors or ADEs. Most studies investigating the effect of CPOE and CDSS on medication errors and ADEs differ substantially in their setting, design, quality and thus, their results [16]. However, it seems that the use of CPOE and CDSS can reduce ADEs [2,16,17]. For example, implementation of CPOE with basic CDSS in two Dutch hospitals reduced the incidence of medications errors but did not demonstrate a direct effect on actual patient harm [9]. In addition, a computerized reminder system that used rules to alert physicians of using four preventive therapies (pneumococcal vaccination, influenza vaccination, subcutaneous heparin and aspirin at discharge) showed a significant increase in the rate of delivery of such therapies [18].

A limitation in our study is the use of chart review to search and detect ADEs. The incidence rates of ADEs have shown to be dependent on the method of detection used [19]. However, we choose chart review because it is a well-known and classical way of adverse (drug) event detection [15,20]. More importantly, studies comparing different methods of ADE detection found that chart review was more effective in detecting events manifested primarily by symptoms, such as change in mental status, nausea and vomiting, rigors and hypotension and less effective in detecting changes in laboratory values [19,21]. Clearly, most ADEs will be found with a combination of methods. For that reason, we used a paper trigger list with symptoms and laboratory abnormalities in combination with review of paper and electronic charts.

Another limitation of our study is that we used two different research pharmacists to perform chart review for the baseline and the intervention period. This may have attributed to the difference in number of ADE between the two periods. But both persons used the same trigger list, same clinical research form and same instruction and the second reviewer, the internal medicine specialist, was the same in both periods. We also did not estimate interrater scores for ADE, causality, severity and preventability assessments. Indeed, the Dutch POEMS

study showed that there was only fair agreement on the assessment of preventable ADEs, and it was suggested that the best practical solution is a combination of a pharmacist and a physician for scoring, like we used in our study [10]. We agree with Haynes et al. that it is still a challenge to assess ADEs incidence in a reliable way [22]. Despite the fact that many other variables such as patient characteristics and setting, may influence ADE rates, we found comparable numbers as reported in the literature. Therefore, we believe that inter observer variability may have played only a minor role in our current study.

In our study confounding bias cannot be ruled out since the performance of the study may have led to more awareness related to medication safety.

A relatively small number of the clinical rules active in the system ADEAS resulted in alerts, and the "potential ADE capture rate" of some clinical rules was not high. Only 9% of the alerts resulted in an action by the hospital pharmacist. The other 91% of the alerts needed no intervention, but frequently dose checks and lab control were performed by the hospital pharmacist. For example a rule regarding the combination of a drug and a declined renal function can result in no intervention when the dosage of the drug is already correctly adapted. But still it is a useful clinical rule with alert that leads to a check by the pharmacist. Maybe our set of clinical rules needs some adaptations and modifications in order to further enlarge the amount of positive alerts, for example special clinical rules for elderly patients or transplantation patients. Adapting the content of the rules during use is an acceptable way to enlarge the positive predictive value for the clinical rules [23]. With smarter clinical rules, the added value of ADEAS in detecting patients at risk can even be increased.

Overall we can conclude that the use of the clinical decision support system ADEAS for the pharmacy which combines patient data and drug information available from multiple sources, helps to reduce preventable ADEs and to improve patient safety.

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7

Evaluation of rule effectiveness and positive predictive value of clinical rules in a Dutch clinical decision support system in daily hospital pharmacy practice

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Abstract

Introduction: Our advanced clinical decision support (CDS) system, entitled 'adverse drug event alerting system' (ADEAS), is in daily use in our hospital pharmacy. It is used by hospital pharmacists to select patients at risk of possible adverse drug events (ADEs). The system retrieves data from several information systems, and uses clinical rules to select the patients at risk of ADEs. The clinical rules are all medication related and are formulated using seven risk categories.

Objective: This study's objectives are to 1) evaluate the use of the CDS system ADEAS in daily hospital pharmacy practice, and 2) assess the rule effectiveness and positive predictive value (PPV) of the clinical rules incorporated in the system.

Setting: Leiden University Medical Center, The Netherlands. All patients admitted on six different internal medicine and cardiology wards were included.

Measures: Outcome measures were total number of alerts, number of patients with alerts and the outcome of these alerts: whether the hospital pharmacist gave advice to prevent a possible ADE or not. Both overall rule effectiveness and PPV and rule effectiveness and PPV per clinical rule risk category were scored.

Study design: During a 5-month study period safety alerts were generated daily by means of ADEAS. All alerts were evaluated by a hospital pharmacist and if necessary, healthcare professionals were subsequently contacted and advice was given in order to prevent possible ADEs.

Results: During the study period ADEAS generated 2650 safety alerts in 931 patients. In 270 alerts (10%) the hospital pharmacist contacted the physician or nurse and in 204 (76%) cases this led to an advice to prevent a possible ADE. The remaining 2380 alerts (90%) were scored as non-relevant. Most alerts were generated with clinical rules linking pharmacy and laboratory data (1685 alerts). The overall rule effectiveness was 0.10 and the overall PPV was 0.08. Combination of rule effectiveness and PPV was highest for clinical rules based upon the risk category 'basic computerized physician order entry (CPOE) medication safety alerts fine-tuned to high risk patients' (rule efficiency = 0.17; PPV = 0.14).

Conclusion: ADEAS can effectively be used in daily hospital pharmacy practice to select patients at risk of potential ADEs, but to increase the benefits for routine patient care and to increase efficiency, both rule effectiveness and PPV for the clinical rules should be improved. Furthermore, clinical rules would have to be refined and restricted to those categories that are potentially most promising for clinical relevance, i.e. 'clinical rules with a combination of pharmacy and laboratory data' and 'clinical rules based upon the basic CPOE medication safety alerts fine-tuned to high risk patients'.

Introduction

Adverse drug events (ADEs) can occur at any point the medication process, from ordering and prescribing to dispensing, reconstitution and drug administration [1,2]. As advanced information technology plays an important role in the improvement of medication safety, we have opted to use one of the technologies available to prevent ADEs [1]. Different of such technologies are described in literature, for example barcode scanning to identify both drugs and patients, use of computerized physician order entry (CPOE) with or without clinical decision support (CDS) system, smart pumps and the use of robots for drug dispensing [3,4]. Although no randomized control trials were performed, there are investigations showing that a reduction in ADEs can be reached by means of using CPOE in combination with CDS systems [5-7]. CDS systems can range from basic to more advanced [8]. Basic CDS systems, for example, include basic dosing guidance or drug–drug interaction checking only. More advanced CDS systems can include dosing support for renal insufficiency and guidance for medication-related laboratory testing [8].

The information system in use in our hospital is Mirador® with incorporated CPOE system Medicatie/EVS® (Medicator®)(iSOFT Nederland BV, Leiden, The Netherlands), is a basic CDS system which provides online basic medication safety alerts [9]. The safety alerts in our CPOE system are retrieved from a Dutch national drug database (the G-Standard). This database contains safety information on all drugs registered in The Netherlands, and provides drug–drug interactions information, duplicate orders and overdoses alerts [10]. In order to reduce the limitations of a basic CDS system such as Medicator® [11-13], we have developed an advanced CDS system, named 'adverse drug event alerting system' (ADEAS). ADEAS is in use in the hospital pharmacy and it is used by hospital pharmacists as medication surveillance tool to select patients at risk of possible ADEs. The system retrieves data from several information systems, and uses clinical rules to select the patients at risk of ADEs. Selection of these patients potentially at risk occurs by combining data from the electronic patient databases (EPD) (laboratory data, patient characteristics), the CPOE (prescribed medication) and the 'G-standard' (National Dutch drug database).

In a previous study, we compared ADEAS with our CPOE with basic CDS system and showed that ADEAS has an additional value in selecting different kind of patients at risk of ADEs. This study showed that the basic CDS system generated safety alerts regarding drug–drug interactions and drug-overdosing only, whereas ADEAS also generated alerts regarding declined renal function and other laboratory abnormalities. It was proven that alerts generated by ADEAS led to a larger number of interventions by pharmacists when compared to alerts generated by the basic CDS system [14].

The objectives of this current study were: (1) to evaluate the use of ADEAS in daily practice as a CDS system for hospital pharmacists; (2) to assess the rule effectiveness and positive predictive value (PPV) of the clinical rules incorporated in the ADEAS system.

Study context

Organizational setting

The study was performed in the Leiden University Medical Center (LUMC), a teaching hospital in Leiden, The Netherlands, forming part of Leiden University. The study was conducted on six clinical wards: haematology (hemat), cardiology (cardio), combined lung/gastrointestinal diseases ward (lung and gastro), short stay internal medicine (short stay) and two combined internal medicine wards, one specializing in endocrinology, nephrology and general internal medicine (called mixed internal 1) and one specializing in infectious diseases, oncology and rheumatology (called mixed internal 2). All patients admitted on these wards during the study period (a 5-month period, from September 2009 up to January 2010) were included in this study, irrespective of their age or the number of different drugs at the time of admission. All included patients were screened on a daily basis by ADEAS throughout their stay in hospital.

System details and full description of system in use

Description of CDS system ADEAS

ADEAS was composed by means of Gaston (Medecs BV, Eindhoven, The Netherlands), which is a guideline-based decision support framework, consisting of both a guideline development module and a decision support module [15,16]. The guideline development module consists of a task network module [17] which describes the structure ('logic' or 'flow') of the guideline by means of a set of primitives (such as observations, decisions, and actions) and which provides domain specific knowledge in the form of one or more terminology items. For the guideline development module, we defined the following terminology items: drug, laboratory values, drug–drug interactions and patient characteristics. The data used for ADEAS can be specified as follows. The data for the 'drug' and 'drug–drug interactions' sections were imported from the national Dutch drug information database (the 'G-standard'). The data regarding laboratory values and patient characteristics were imported from the hospital information system, Glims® (MIPS Diagnostics Intelligence, Clinisys, UK) and Mirador®. The information about drug use for specific patients was imported from the CPOE, Medicator®.

A decision support module was used to link Gaston with our hospital information system in order to be able to import the required information and to execute the clinical rules. Gaston was originally designed as a CDS system within a CPOE. We, however, preferred to use ADEAS as a pharmacy decision support system, not incorporated in the CPOE. This resulted in technical adaptations to the reporting technology.

The primitives and terminology items were combined and used to create and integrate the clinical rules into the system. The terminology items were moved to the desired field (positive or negative preferences). Per item, sub items such as dosage or administration route for a drug could be added. Most clinical rules consisted of simple observations of one or more positive and/or negative term preferences, for example a drug prescription and the presence of a laboratory value or a drug prescription and the absence of a laboratory value. More complicated clinical rules were built as a flowchart using the primitives. We started with a set of 121 clinical rules. Figure 7.1 offers the reader insight in ADEAS and gives the reader an example of how clinical rules were formed.

More detailed information about the development and validation of our system including the first set of clinical rules has been described elsewhere [18].

Description of clinical rules

The contents of the clinical rules were established with the help of a multidisciplinary team. From a drug perspective seven risk categories were defined which were used to create clinical rules. For each drug or drug class, the seven risk categories were discussed and this, subsequently, resulted in agreement and definition of a clinical rule [18]. The seven risk categories specified by the multidisciplinary team are:

1. Combination of biochemical laboratory values with the initiation of drug use
   Examples of clinical rules: A) patient start with an aminoglycoside and the estimated glomerular filtration rate (eGFR) < 50 ml/min, B) patient start with lithium and eGFR < 50 ml/min, C) patient start with allopurinol > 200 mg and eGFR < 50 ml/min, and D) no international normalized ratio (INR) 3 days after start phenprocoumon.
2. Combination of biochemical laboratory values or therapeutic drug monitoring values with the ongoing use of a drug
   Examples of clinical rules: A) patient with sotalol > 160 mg and eGFR decline below 50 ml/min, B) INR > 6 during use of coumarin anticoagulant, and C) no therapeutic drug monitoring 2 days after start or dosage change of aminoglycoside or vancomycin.
3. Combination of use of a drug with non-use of a drug, the latter indicated for the prevention of an ADE

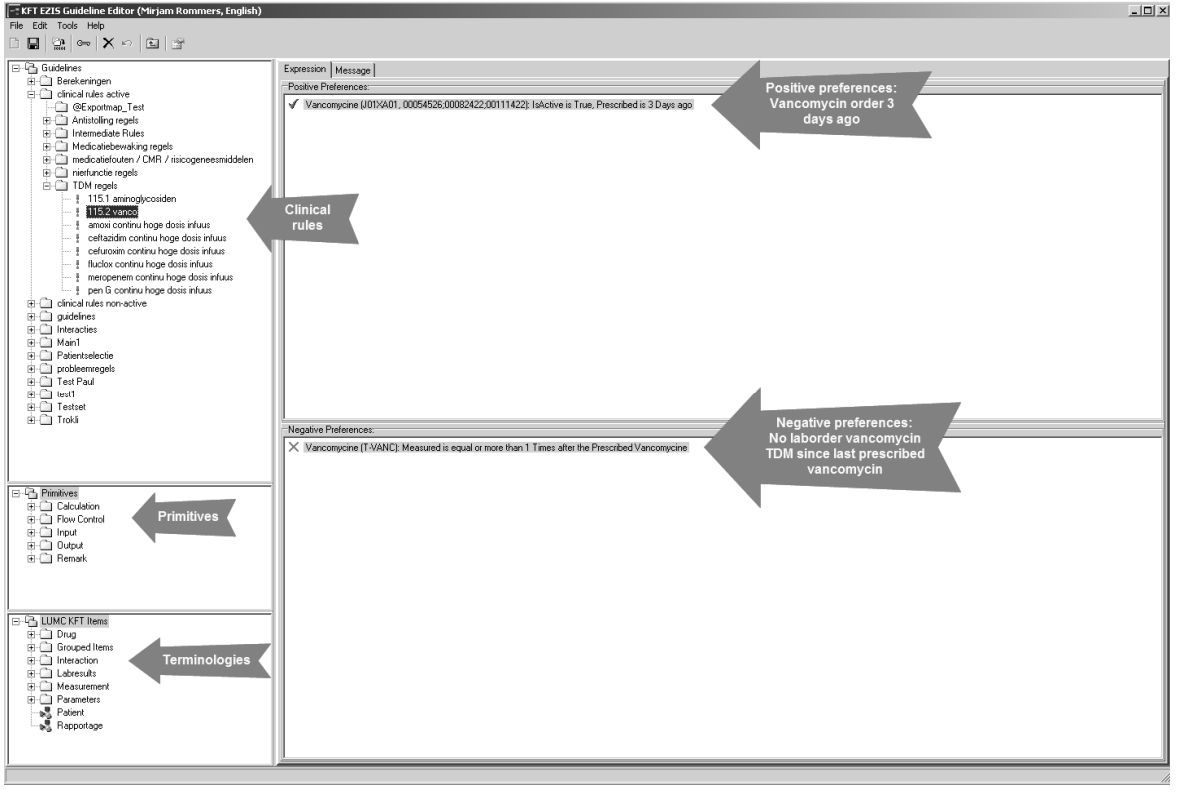

Figure 7.1 Example of how the clinical rule 'no therapeutic drug monitoring 2 days after start vancomycin' is created in Gaston-ADEAS.
The terminology item 'drug-vancomycin' is moved to the positive preferences field. A sub item 'prescribed t3 days ago' is added. The terminology item 'lab result-vancomycin therapeutic drug monitoring' is moved to the positive preferences field. A sub item 'prescribed 3 days ago' is added. The terminology item 'lab result-vancomycin therapeutic drug monitoring' is moved to the negative preferences field. A sub item 'measured 1 time after last prescribed vancomycin' is added.

Examples of clinical rules: A) patient with co-trimoxazole and no folic acid, and B) patient with opioid agonist of > 2 days and no laxative.

4. Medication used to treat an ADE
   An example of a clinical rule: A) patient with inhibitor of angiotensin converting enzyme (ACE-inhibitor) and anti-cough medication.
5. Basic CPOE medication safety alerts fine-tuned to high risk patients
   Examples of clinical rules: A) patient with a quinolone antibiotic and interacting co-medication regarding absorption, B) patient with drug–drug interaction between non-steroidal anti-inflammatory drug (NSAID) and ACE-inhibitors or angiotensin receptor blockers (ARBs) and eGFR < 50 ml/min, C) patient with anti-epileptic medication and start a quinolone antibiotic, and D) Patient with start aminoglycoside and prescription of cisplatin in previous 6 months.
6. Safety alerts from inspection authority
   Examples of clinical rules: A) patient with azathioprine in dose > 150 mg/day, and B) patient with methotrexate in non-weekly dose schedule.
7. Medication errors and high risk drug situations
   Examples of clinical rules: A) patient > 80 years of age and Beers-list medication, B) patient with aspirin low dose and co-medication with ulcer risk and no proton pump inhibitor, and C) patient with gastrointestinal tube.

Methods

Study design

The evaluation of ADEAS was investigated in a prospective non-randomized observational study. All patients admitted on one of the six wards used for this study were screened on a daily basis by ADEAS throughout their stay in hospital. ADEAS was used as a CDS system by the hospital pharmacist to select patients at risk of possible ADEs. The system ran every night selecting patients potentially at risk based upon the clinical rules. The output was generated in the pharmacy department every morning. Every day (except during weekends; safety alerts produced during weekends were read on Mondays) all the safety alerts were reviewed in detail by one of the hospital pharmacist. Additional case specific information was subsequently collected for each patient in the EPD to assess the clinical relevance of the alert for that specific patient. Consequently, if necessary, the hospital pharmacist contacted the physician or nurse to give advice or to intervene.

Outcome measures

To evaluate the use of the ADEAS system for daily hospital pharmacy practice the following items were scored: 1) the total number of alerts generated by ADEAS, 2) the number of patients with an alert, and 3) the outcome of the alerts; whether the hospital pharmacist gave advice to prevent a possible ADE or not. Of all the advice given by the hospital pharmacist the type of advice was scored. In addition, the percentage of acceptance of the advice by the healthcare professional was scored as well.

The rule effectiveness and PPV of all the rules triggered in ADEAS, and of each rule risk category separately, were calculated.

Measurement

To measure the outcome of the alerts, all ADEAS alerts were divided into the following categories:

Alert category (1) alert considered non-relevant.
After detailed review by the hospital pharmacist of the alert (for example, after dose check or laboratory value check in the EPD), the alert was considered not clinically relevant for this specific patient.

Alert category (2) alert resulting in contact with physician or nurse.
After review of the alert, the hospital pharmacist contacted the healthcare professional (by phone or by means of personal advice, while visiting the ward) in order to discuss the alert and get further clarification about the reasons for prescribing. This contact may or may not lead to an advice to adjust treatment in order to prevent possible ADEs.

Alert category (3) alert with advice/intervention.
Category 3 includes all actual advice given after contacting the healthcare professional.

If advice was given by the hospital pharmacist, the following types of advice were distinguished: 1) advice to adjust the dose; 2) advice to discontinue or suspend medication; 3) advice to change medication; 4) advice to continue medication but to monitor side effects; 5) advice to adjust the time drugs are administered; 6) advice to add extra medication; and 7) advice to initiate drug blood level measurement or other laboratory control such as renal function.

To measure the acceptance rate of all advice given, we checked the documented modification in therapy. The hospital pharmacist who gave the advice checked the patient's EPD the following day in order to ensure that the advice was adhered to.

All generated alerts were specified according to one of the seven risk categories for the clinical rules, described above [18]. Both the overall rule effectiveness and PPV and the rule effectiveness and PPV per rule risk category were scored. A measure of rule effectiveness is the ratio of the number of alerts resulting in contact with healthcare professional to the total number of alerts generated by ADEAS. We used rule effectiveness as a variant of rule efficiency. Rule efficiency is the probability of an alert leading to action of by the pharmacist [19]. The PPV is the probability of an alert leading to advice/intervention. The PPV was calculated by the quotient of the number of advice/interventions to prevent a possible ADE and the total number of alerts generated by ADEAS [19].

Results

Results number of alerts and alert outcome

During the 5-month study period (September 2009 – January 2010) ADEAS generated a total of 2650 alerts for 931 patients. This is a mean of 17 alerts per day. The main results are shown in Table 7.1 and Figure 7.2. Most alerts, 2380 (90%) out of 2650, were rated as alerts for category 1 (alert considered non-relevant). In 270 (10%) out of these 2650 alerts, the hospital pharmacist contacted the physician or nurse (alert category 2). In 204 (76%) out of these 270 alerts, the pharmacist gave advice to prevent the possible ADE (alert category 3). For 204 times advice was given, 128 instances were accepted by the healthcare

Table 7.1 Main results: number of alerts with ADEAS, alerts outcome and overall rule effectiveness and PPV

Total number of alerts	2650
Total number of patients with alerts	931
Number of alerts, alerts category 1 (alert considered non-relevant)	2380 (90%)
Number of alerts, alert category 2 (alerts resulting in contact with prescriber or nurse)	270 (10%)
Number of alerts, alert category 3 (alert with advice/intervention)	204 (7.6%)
Number of alerts for which advice was given and adhered ti	128 (4.8%)
Rule effectiveness (overall)	270/2650 = 0.10
PPV (overall)	204/2650 = 0.08

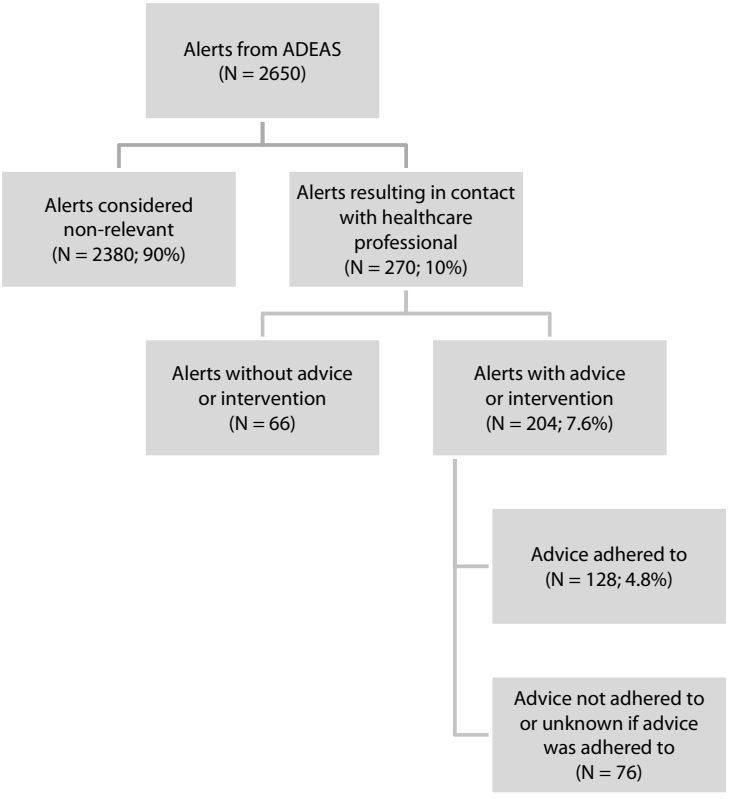

Figure 7.2 Main results: number of alerts with ADEAS and alert outcome.

professionals. For the remaining 76 times advice was given, advice was either not adhered to or it is not clear whether advice was adhered to. In total, 128 (4.8%) out of 2650 alerts led to a documented modification in therapy. The alert outcome representing the spread over the study wards is shown in Figure 7.3.

All advice given by the hospital pharmacists is specified in Table 7.2. Sometimes there was more than one type of advice given following an alert, for example, to both add medication and monitor for side effects.

Results rule effectiveness and PPV

The overall rule effectiveness of ADEAS was 0.10 (270/2650) and the overall PPV was 0.08 (204/2650) (Table 7.1).

Most alerts, 963 alerts, were generated by clinical rules from risk category 1 ('Combination of biochemical laboratory values with the initiation of a drug'). Clinical rules from risk category 2 ('Combination of biochemical laboratory values or therapeutic drug monitoring values with the ongoing use of a drug') generated 722 alerts. Clinical rules from risk category 5

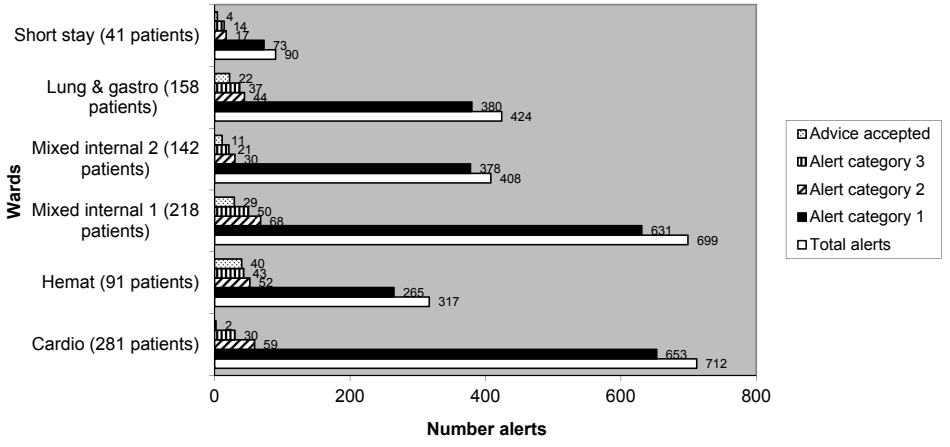

Figure 7.3 Results number of alerts with ADEAS and alert outcome divided between different wards.
Total alerts: total number of alerts generated by ADEAS (category 1 + category 2)
Alert category 1: number of alerts considered non-relevant
Alert category 2: number of alerts resulting in contact with physician or nurse
Alert category 3: category 3 includes all actual advice given after contacting the healthcare professional
Advice accepted: number of alerts from category 3 for which advice was given by hospital pharmacists and adhered to by the healthcare professionals

Table 7.2 Type of advice given following alerts from ADEAS

Type of advice	Number of alerts
Dose adjustment	67
Discontinue or suspend medication	12
Change medication	13
Monitor side effects	9
Take drugs separately/adjust administration time	45
Add medication	37
Measure drug blood lever or other laboratory control	34

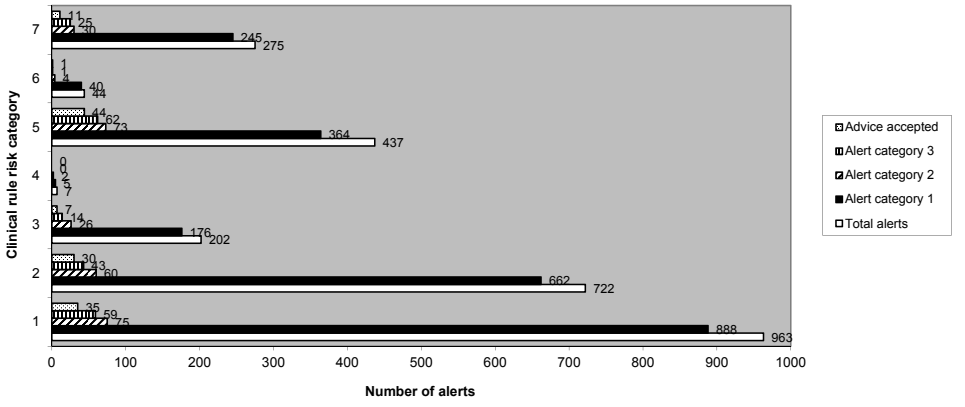

Figure 7.4 Results number of alerts with ADEAS and alert outcome divided per clinical rule risk category.

Total alerts: total number of alerts generated by ADEAS (category 1 + category 2)

Alert category 1: number of alerts considered non-relevant

Alert category 2: number of alerts resulting in contact with physician or nurse

Alert category 3: category 3 includes all actual advice given after contacting the healthcare professional

Advice accepted: number of alerts from category 3 for which advice was given by hospital pharmacists and adhered to by the healthcare professionals

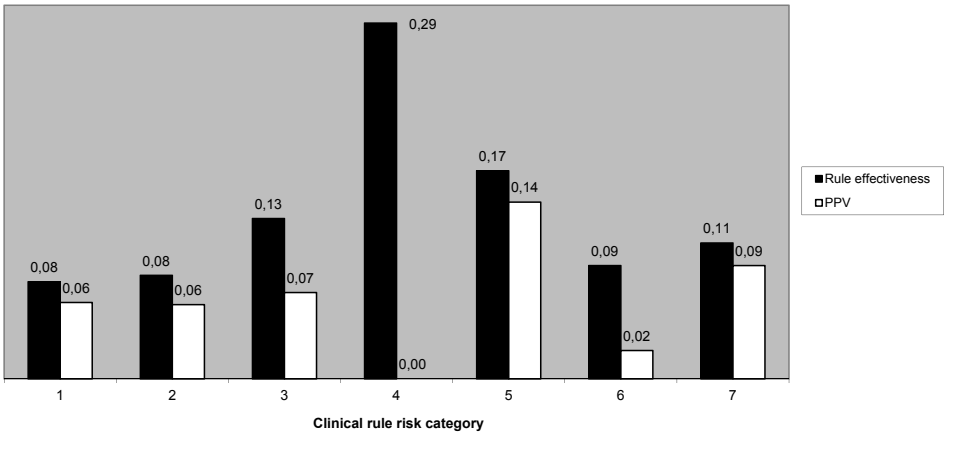

Figure 7.5 Results rule effectiveness and PPV per clinical rule risk category.

Rule effectiveness: the ratio of the number of alerts resulting in contact with physician or nurse tot the total number of alerts generated by ADEAS.

PPV (positive predictive value): the quotient of the number of advices/interventions to prevent a possible ADE and the total number of alerts generated by ADEAS.

('Basic CPOE medication safety alerts fine-tuned to high risk patients') generated 437 alerts. In Figure 7.4, the alert results per clinical rule risk category are shown. The PPV was highest for clinical rules from risk category 5 (0.14). Rules from this category had the second highest rule effectiveness score (0.17). Consequently, this category had the highest combination of rule effectiveness and PPV. Figure 7.5 shows all the results for rule effectiveness and PPV.

An extra ordinary result is the high rule effectiveness of 0.29 for rules from category 4 ('Medication used to treat an ADE') together with a PPV of zero. This rule category covered one clinical rule (Patient with an ACE-inhibitor and anti-cough medication) and resulted in 7 alerts during the study period. In two instances, the pharmacist contacted the physician but this never led to an advice. This rule can be considered of low clinical relevance.

Discussion

Answer to study questions

In this study we evaluated the usefulness of the CDS system ADEAS for selecting patients at risk of ADEs in daily hospital pharmacy practice. The main result of this study is that the ADEAS system can be used for this goal, but that both rule effectiveness and PPV would have to be increased in order to use the ADEAS system effectively. The overall rule effectiveness score was 0.10. This means that 10% of the safety alerts generated by means of ADEAS resulted in direct contact by hospital pharmacist and healthcare professional. The overall PPV was 0.08. This means that 7.8% of the alerts resulted in advice or intervention to prevent possible ADEs. In addition, the majority of advice given by the pharmacist was accepted. ADEAS is considered most useful with rules from risk category 1, 2 and 5, because those rules had the highest combination of rule effectiveness and PPV (risk category 5) and the highest number of alerts (risk categories 1 and 2). This is explained in more detail in Section 5.4 of this paper.

A rule effectiveness of 0.10 implicates that a large number of alerts (90%) were scored as non-relevant (alert category 1). The authors feel it is important to comment that all alerts considered in this study could have led to potential ADEs, but that in certain cases, alerts were rated as non-relevant, after detailed review of the patient's EPD. There are a few of such situations in which an alert was considered non-relevant: 1) one such example is an alert generated by the clinical rule regarding the use of a quinolone antibiotic and a declined renal function (eGFR < 30 ml/min). It could be that the physician in this specific case had already

adjusted the dose himself, taking into consideration the patient's renal function. In that case, the hospital pharmacist actively checked the patient's EPD following the alert, but found that the alert was non-relevant because dose adjustment had already taken place; 2) another example is an alert generated by the clinical rule regarding absence of INR laboratory results during phenprocoumon therapy. It could be that the INR laboratory control was ordered the day the pharmacist reviewed the alert, but that the results were not yet known by that time. Because it was clear to the pharmacist that laboratory control of INR had already been ordered, the pharmacist rated the alert as non-relevant; 3) another situation in which the pharmacist considered an alert as non-relevant that can easily be explained occurred on the cardiology ward. Most patients at this ward received an intervention procedure, such as implantation of an implantable cardioverter defibrillator or a percutaneous transluminal coronary angioplasty. These patients often have a short period of declined renal function and high INR values after the procedure but, however, it is known that values improve quickly. In those cases, alerts do not lead to intervention and medication does not need to be adjusted; and 4) a last reason for considering alerts as non-relevant is the fact that alerts reappear for the same patient – the alerts are then counted and included in the total number, but intervention only has to take place once.

All reasons mentioned above are related to the low sensitivity and or low specificity of the created clinical rules in ADEAS. In some cases the clinical rules were adapted during the study, to enlarge their sensitivity or specificity. To lower the number of non-relevant alerts, both rule effectiveness and PPV of ADEAS should be increased in the future. One possible adjustment is to add more sub items to a rule. For example the sub item 'drug dosage' can be added in a rule regarding drug use and declined renal function. Or the sub items 'ward' or 'specialty' can be added in a rule considered not relevant for specific patient categories. In addition, the authors recommend that a technical solution should be found to lower the amount of duplicate alerts. This can be achieved by including a sub item that takes into consideration the previous alerts generated for the same patient. In order to increase the effectiveness of ADEAS for routine patient care, it can be concluded that the clinical rules have to be refined and potentially restricted to those categories that are clinically relevant.

Strengths and weaknesses of the study

One of the main strengths of our study is that ADEAS was tested and evaluated in the actual clinical setting it was intended for: in routine daily practice, and not just in a research setting. This makes the evaluation highly clinically valuable and the results very useful and

significant. Actually testing ADEAS in the actual clinical setting meant that the result could be applied directly in clinical practice.

A limitation of our study is that we did not measure ADEs as endpoint. Had we done so, we could have said more about the ability of ADEAS to prevent actual ADEs. In a study not yet published, we investigated the effect of ADEAS on ADEs. Studying a subpopulation consisting of elderly patients with polypharmacy, it was proven that the use of ADEAS resulted in a significantly lower number of preventable ADEs. ADEAS did not have an effect on the total number of ADEs (unpublished data). Our current study is a prospective observational study to evaluate the use of ADEAS in daily practice and measurement did not include ADEs.

Another limitation of our study is that we only based the advice acceptance rate on documented modifications in therapy. The acceptance rate was measured by checking the EPD of the patient the next day to verify if the advice was adhered to. We did not interview the healthcare professional for a complete follow-up, however. We scored a total of 76 (37%) out of 204 advices by the hospital pharmacist, for which advice by the hospital pharmacist was either not adhered to or for which it was unknown whether advice was adhered to. In many cases the acceptance rate could not be verified in the documentation because the patient had already been discharged the following day; this is often the case on the cardiology ward or on the short stay ward, where patient turnover is high. At the cardiology department only 2 out of 30 instances of advice were scored as accepted, and at the short stay ward 4 out of 14. Moreover, the advice 'monitor side effects' (given in 9 cases) could not be verified either, because it was not a documented modification in therapy. This could be a possible explanation why the acceptance rate of 63% is rather low compared to other investigations. Two studies in which pharmacists gave dosages advice in case of impaired renal function showed an acceptance rate of 74% (141 of 191 recommendations accepted) and 88% (142 of 162 recommendations accepted) respectively [20,21]. In addition, the study of Silverman et al. reported an acceptance rate of 78.7%, 90.9% and 92.2% in their three different study periods [19].

Finally, another minor limitation of our study is that we did not consider the time element. With time measurement a better judgment can be made whether the found PPV and rule effectiveness is worthwhile for the efforts of the hospital pharmacist. We did measure time for a study that has not yet been published, also mentioned above, regarding a subpopulation consisting of elderly patients with polypharmacy. The amount of time measured required for ADEAS was an acceptable maximum of approximately 1 hour per day per hospital (unpublished data).

Results in relation to other studies

The percentage of safety alerts resulting in advice or intervention by the hospital pharmacist (10%) seems low, but is comparable to or even higher than other international investigations. Jha et al. investigated a commercial computerized surveillance system and found that in 30 (11.3%) out of 266 reviewed alerts the physician was contacted [22]. During a two month period, Kilbridge et al. evaluated 4604 triggers from a computer-based ADE surveillance system with rules of which 206 led to an intervention (4%) [23]. The intervention percentages found by Silverman et al. with their computer-based monitoring system with rules ranged from 5% to 13% [19]. In an earlier study we compared ADEAS with our conventional medication surveillance using only safety alerts from the Dutch national database G-Standard (basic CPOE safety alerts). The percentage of interventions with ADEAS was three times as high [14].

From our study, we can conclude that the variation of rule effectiveness and PPV among the categories of clinical rule was highly variable. However, this is observed in the literature as well. Kilbridge et al. reported a widely varied PPV, ranging from 0.00 to 0.67. The rule efficiency varied between 0.00 and 0.21. The highest PPV values were found for rules detecting ADEs (e.g. antidote order). The rules detecting evolving unsafe situations had lower PPV [23]. We did not use clinical rules triggering on antidote orders. Comparable numbers for PPV are found in the study by Silverman et al. The rule efficiency varied between 0.05 and 0.13. The authors determined that a realistic goal for created rules was a rule efficiency of 0.10 and an idealistic goal a rule efficiency of 0.20 [19]. Our rule effectiveness and PPV of ADEAS were 0.10 and 0.08 respectively. In themselves, these are promising figures indeed, but these figures could be increased if appropriate measures, such as enlarging the sensitivity or specificity of our clinical rules, are taken.

Meaning of the study

The combination of rule effectiveness and PPV was highest for clinical rules based upon the basic CPOE medication safety alerts fine-tuned to high risk patients. The safety alerts in the CPOE are retrieved from the Dutch national drug database (the G-Standard). This database is used as a knowledge base for all pharmacy systems and CPOE systems within hospitals in The Netherlands. A problem with the safety alerts (drug–drug interactions, duplicate orders and overdosages) is that they are frequently overridden due to low specificity. The safety alerts also have low sensitivity [12,13]. In our own specifically designed set of clinical rules, we have fine-tuned these safety alerts to patients at risk of ADEs. For example, the safety alert for patients using the combination of a NSAID and ACE-inhibitors or ARBs is

most effective when considered in relation to the kidney function of the individual patient. In the basic CPOE a safety alert is always generated when the combination of the two drugs are prescribed. With ADEAS, the combination only generates an alert if the patient has a declined renal function (eGFR < 50 ml/min). This makes the drug–drug interaction alert more clinically relevant. ADEAS takes into account the renal function of the patient, where the basic CPOE does not. It is clear from this example that using ADEAS is preferred to using a basic CPOE only. Another example is a drug–drug interaction between a NSAID and a corticosteroid. The basic CPOE safety alert is generated always when both drugs are prescribed. ADEAS only generates an alert when a drug for ulcer prevention is absent. ADEAS takes into account the co-medication of the patient, while the CPOE does not. The use of this category of clinical rules improves the specificity of the alerts and therefore may help to decrease alert fatigue. That some other investigators have used this approach as well underlines the importance and usefulness of such an approach [24-26]. For example Seidling et al. suggests refining drug–drug interactions with statin-drugs by using an upper dose limit [25]. And Riedmann et al. searched for context factors, such as patient, prescriber/ward or alert characteristics, to prioritize drug–drug interactions [24].

In our study the highest number of consult and advice were given following alerts from clinical rules related to laboratory values (risk categories 1 and 2). This is in line with the observations in two of our other studies that show that the clinical rules linking laboratory and pharmacy information improve the sensitivity of the medication surveillance [14,27]. Other investigations also show that clinical rules related to laboratory values are suitable clinical rules that offer good results in detecting and preventing ADEs [20,21,28-30]. In our study the clinical rules related to laboratory values generated more than 50% of the alerts. They can be considered as most useful and promising rules. But as mentioned before, for better performance the rule effectiveness and PPV should be increased.

In the future we should focus on clinical rules from the three risk categories 1, 2 and 5 ('clinical rules with a combination of pharmacy and laboratory data' and 'clinical rules based upon the basic CPOE medication safety alerts fine-tuned to high risk patients') to enhance the performance of ADEAS.

Conclusion

In conclusion, the CDS system ADEAS can effectively be used in daily hospital pharmacy practice to select patients at risk of potential ADEs, but to increase its benefit for routine patient care and to increase efficiency, both rule effectiveness and PPV for the clinical rules

should be improved. Furthermore, clinical rules would have to be refined and restricted to those categories that are potentially most promising for clinical relevance, i.e. 'clinical rules with a combination of pharmacy and laboratory data' and 'clinical rules based upon the basic CPOE medication safety alerts fine-tuned to high risk patients'.

Acknowledgements

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Part V

Discussion & summary

8

General discussion

Adverse drug events (ADEs) occur frequently in hospitalized patients, can result in harm but can often be prevented [1]. Many different methods to prevent ADEs are recognized [2-4] and two preventive strategies are the focus of this thesis, namely 1) computerized physician order entry (CPOE) with clinical decision support system (CDSS), and 2) clinical pharmacist activities.

Although no randomized controlled trials have been performed, several investigations have shown that a reduction in ADEs can be reached through the use of CPOE with CDSS [5-7]. A Dutch study showed that implementation of a CPOE with basic CDSS reduces certain types of medication errors (such as dosing errors and administrative and procedural errors). This study did not demonstrate a direct effect on actual patient harm [8].

At our institution, Leiden University Medical Center, the site where we performed our studies, a CPOE with basic CDSS is in use since 2003. This system, named Medicator® (iSOFT Nederland, Leiden, The Netherlands), gives basic drug-drug interaction and drug-dosing alerts to the physician while prescribing medication and can in that way prevent some medication errors and ADEs [9]. This is called conventional medication surveillance.

In the current thesis our hypothesis is that the use of a more advanced CDSS incorporating clinical rules can improve the indentification of patients at risk of ADEs. These clinical event-monitoring systems can use any data available in electronic form to detect potential ADEs and risk situations. The clinical rules or algorithms are based on identifiers which search for specific medication orders, patient characteristics and/or laboratory values. In addition, hospital pharmacists can interfere to prevent ADEs and, as such, improve medication safety. The development of this system, named Adverse Drug Event Alerting System (ADEAS) is the basis of this thesis. We have chosen to combine our two fields of interest to prevent ADEs: CDSS for identifying patients at risk of ADEs and hospital pharmacist intervention focused on these specific patients at risk instead of participation on ward rounds.

In this part of this thesis we highlight and critically discuss the following aspects of our advanced CDSS ADEAS (Figure 8.1):

- Development and validation of the CDSS ADEAS ('analytical validity')
- Ability of ADEAS to detect patients at risk of ADEs ('clinical validity')
- Ability of ADEAS guided interventions by hospital pharmacists to prevent ADEs ('clinical utility')
- Future perspectives of ADEAS and clinical rules

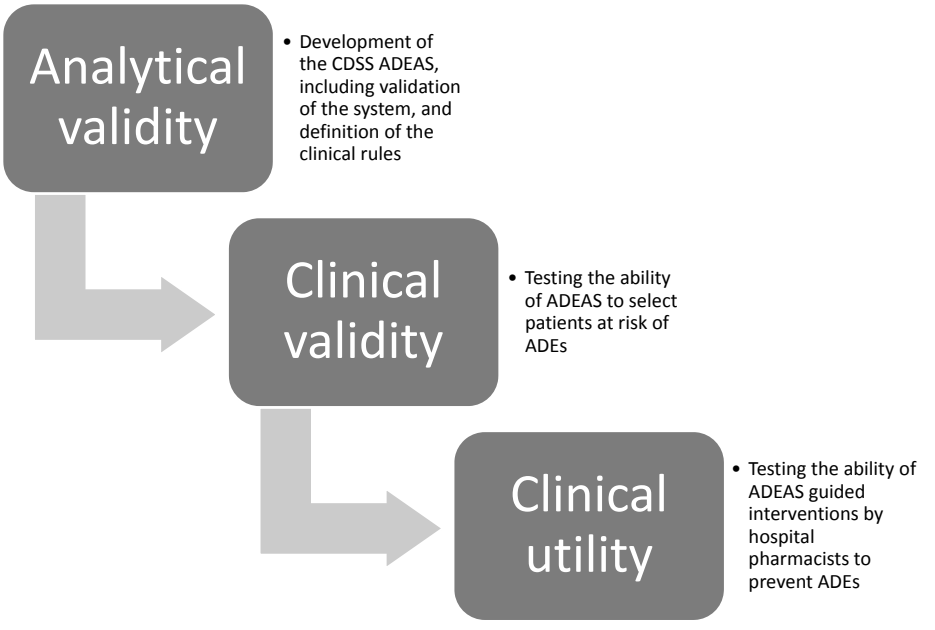

Figure 8.1 Outline discussion.

Analytical validity

First in **chapter 3** we show that we successfully developed and validated an advanced CDSS ADEAS. ADEAS is based on Gaston software (Medecs, Eindhoven, The Netherlands), which is a guideline-based decision support framework. The definition of the clinical rules by a multidisciplinary team resulted in a comprehensive set of 121 clinical rules with a wide clinical coverage.

A strong aspect of our CDSS ADEAS is that it gathers information from more databases available in the hospital compared to our basic CDSS within the CPOE. Not only data regarding patient drug prescriptions and drug-drug interaction data from the Dutch drug database 'G-standard' (Z-Index BV, The Hague, The Netherlands) are gathered, but also data regarding patient laboratory values and other data from the electronic patient file (EPF), like age and weight. In particular the use of laboratory data is of added value in clinical rules [10]. Laboratory and pharmacy functions are closely related. Drug choice and dosing often depend on laboratory information such as therapeutic drug levels and biochemical and other physiologic parameters, such as renal function. Despite this relation between laboratory

and pharmacy, connection between their clinical information systems is often suboptimal or non-existent [10], as is the case in our CPOE with basic CDSS. ADEAS is a solution for this problem. The clinical rules in ADEAS can combine prescription and laboratory data. Indeed, several studies have demonstrated that drug-laboratory combinations are one of the best tools for identifying (potential) ADEs [11-14]. Types of ADEs that can be prevented by use of such clinical rules are for example: too high a dose of a drug in a patient who suffers from a declined renal function [15,16], prescribing potassium supplementation to patients despite high potassium levels [17] and lack of laboratory value monitoring (e.g. liver function tests) at the initiation of drug therapy [18].

Unfortunately other potential useful data from the EPF such as microbiology data and medical diagnosis were not included in the clinical rules in ADEAS, because coded data on those items were not available yet. Also laboratory results of (pharmaco)genetic tests can be of use in clinical rules. We suggest to make these data available in the future so we can also use them in ADEAS, resulting in more potential useful clinical rules.

Furthermore in **chapter 3** we describe our structured methodology for defining the clinical rules. We used seven risk categories to create the clinical rules. These seven risk categories are:

1. Combination of biochemical laboratory values with the initiation of a drug
2. Combination of biochemical laboratory values or therapeutic drug monitoring values with the ongoing use of a drug
3. Combination of the use of a drug with the non-use of another drug, the latter indicated for the prevention of an ADE
4. Medication used to treat an ADE
5. Basic CPOE medication safety alerts fine-tuned to high risk patients
6. Safety alerts from inspection authority
7. Medication errors and high risk drug situations

A multidisciplinary team discussed all drugs and drug classes from the Dutch national formulary (Farmacotherapeutisch Kompas, College voor Zorgverzekeringen, Diemen, The Netherlands) to formulate clinical rules on the basis of these seven risk categories. Finally this resulted in incorporation of 121 clinical rules in ADEAS (**appendix chapter 3**). We choose this thorough method because we intended to build an advanced CDSS that, in time, can replace our conventional medication surveillance, the basic CDSS within the CPOE. The seven risk categories fully match with the concept to create clinical rules which search for evolving unsafe situations, except for risk category 4 (Medication used to treat an ADE). These rules detect situations in which an ADE has already occurred and harm cannot be

prevented anymore. Consequently we have deleted the clinical rules belonging to this risk category in current practice.

The development of the system itself was time-consuming and required considerable technical support. Currently available CPOE systems on the Dutch market are not integrated with sophisticated CDSS, and of the few CDSS available, like Gaston, none did match the exact specifications essential for the application we were aiming for. This is the reason why many technical adaptations were necessary. An important disadvantage of this is that it makes such a home-grown CDSS difficult to replicate and implement in other institutions. Nevertheless the concept is still very useful for other hospital pharmacies. Although similar computerized alert systems are developed in the United States [19] and Europe [20], they are not available in The Netherlands. Until now there was limited experience with the development of such systems within Dutch hospital pharmacies. Fortunately knowledge about CDSS and clinical rules in hospitals and at software manufacturers is growing.

A technical validation was necessary to establish wether the system works according to the specification and our expectations. A validation program was developed and written because there are no existing guidelines for validation of a CDSS like ADEAS. We choose three different methods for the validation of ADEAS: 1) by use of dummy patients in the CPOE, 2) testing ADEAS in an off-line test setting, and 3) behind-the-scene testing of ADEAS and manual check of the results with the EPF. These three validation methods were necessary to validate all aspects of the clinical rules; all used terminology items (drug, laboratory values, drug-drug interactions, and patient characteristics) and all the different structures ('logic' or 'flow') used to build a clinical rule in ADEAS. Because of the large number of clinical rules (121), the validation process was complex and time-consuming. However, it is a necessary investment to guarantee a good quality of the system. In the future new clinical rules which are built in ADEAS and use an already validated terminology item and an already validated structure can be used directly in clinical practice and don't need a comprehensive validation. When new terminology items are used in a clinical rule, e.g. medical diagnosis or pharmacogenetic laboratory data, the rule has to be validated before it is used in clinical practice according to one of the three described validation methods.

Chapter 4, 6 and 7 describe different clinical studies in which we investigated the clinical validity and clinical utility of ADEAS. From these studies we have concluded that only a small number of the 121 clinical rules incorporated in ADEAS resulted in alerts. In this respect it would have been better to start with a smaller more clinically relevant set of clinical rules. A useful alternative strategy can be to start with a set of clinical rules covering a specific

drug class known with a high frequency of preventable ADEs. Different studies showed that drug classes often associated with ADEs are analgesics, antibiotics, cardiovascular agents and anti-coagulants [11,21-25]. Another possible strategy is to focus on clinical rules categories known to effectively select potential ADE situations. As mentioned before, several studies have demonstrated that drug-laboratory combinations are one of the best tools for identifying (potential) ADEs [12-14,26]. Following that strategy we would have developed a set of clinical rules only covering our risk category 1 (combination of biochemical laboratory values with the initiation of a drug) and risk category 2 (combination of biochemical laboratory values or therapeutic drug monitoring values with the ongoing use of a drug) instead of all seven risk categories. A simulation learns us that this would have resulted in a set of about 60 instead of 121 clinical rules. Even more specificly, an alternative interesting strategy is to primarily focus on drug dosing in patients who suffer from a declined renal function [15,16].

Resuming, "start low and go slow" would have been a better strategy to formulate the clinical rules, instead of our comprehensive method.

Clinical validity

To investigate the ability of ADEAS to detect patients at risk of ADEs, the 'clinical validity', we compared ADEAS with other detection methods. First in **chapter 3** we performed a proof of principle test. In **chapter 4** we compared ADEAS with our conventional medication surveillance, the basic CDSS within our CPOE, and in **chapter 5** we compared ADEAS with manual chart review by a clinical pharmacist.

In **chapter 4** the results of the retrospective and prospective comparison of ADEAS with our conventional medication surveillance, the basic CDSS within our CPOE, showed that ADEAS detects different kind of patients at risk of ADEs compared to the conventional medication surveillance method. This is a confirmation of the results which we found in the proof of principle test in which we retrospectively compared 13 clinical rules in ADEAS with our conventional medication surveillance (**chapter 3**).

The safety alerts generated by the CPOE with basic CDSS are retrieved from the G-standard, which is a national drug information database. These are safety alerts regarding drug-drug interactions and drug-overdosing. ADEAS generates alerts regarding a declined renal function or other laboratory abnormalities, the absence of essential concurrent medication to protect the patient for ADEs, and for example the use of a gastrointestinal tube. Our clinical validity studies showed that, in particular, clinical rules related to unadjusted drug

dosages in patients who suffer from a declined renal function are important triggers for potential ADEs. This is in line with the findings of other investigators [14-16]. The added value of the new ADEAS system is also illustrated by the rule 'opioid receptor agonist and no prescription for laxative'. This rule gave a high number of alerts, both in the retrospective and prospective studies, whereas this high risk situation is not detected using the conventional medication surveillance method.

Also, the added value of the new ADEAS system is illustrated by a clinical rule regarding the prescription of a NSAID in a patient with a risk factor for ulcer-related bleeding and without a prescription for a proton pump inhibitor. The conventional medication surveillance system does generate an alert in for example a patient with the combination of a NSAID and a SSRI or corticosteroid. But in contrast to ADEAS the basic CDSS within the CPOE cannot take into account the age of the patient or the concurrent medication. Thus even if the patient uses a proton pump inhibitor the physician receives a safety alert. In this situation the basic CDSS within the CPOE generates many false positive alerts, which may lead to alert fatigue by the physician [27,28]. ADEAS only generates an alert when a proton pump inhibitor is absent and the patient is over the age of 70.

It is obvious that ADEAS has an added value in detecting patients at risk of potential ADEs compared with the conventional medication surveillance. However, we should realize that not all safety alerts from the G-standard are built in ADEAS. We did not create clinical rules regarding overdosing covering all drugs and we did not incorporate all drug-drug interactions from the G-Standard. This means that the two systems are used concurrently for the time being: the basic CDSS within the CPOE for overdosing alerts and some basic drug-drug interaction alerts and ADEAS for the fine-tuned clinical rules. Our primary goal for the future is to integrate both systems. By doing so we should realize that the clinical validity of the alerts generated by the G-Standard are assessed by a different method compared to the clinical validity of ADEAS [29].

There are many methods for the detection of (potential) ADEs, but none is considered the golden standard. ADEs were originally detected by means of voluntary report and chart review [21,25]. With the aid of modern information technology, computer-based monitoring systems, such as basic CDSS within the CPOE and systems such as ADEAS, have become more prominent detection methods [12,23,30,31]. With both manual chart review and computer-generated signals high rates of ADEs can be found [32]. On the other hand, voluntary report is still considered to be the method of choice for permanent error detection in hospitals. This is mainly due to the fact that it is less time-consuming, but it is

not the best strategy to detect patients with ADEs, because of the risk of underreporting. That is why we choose to compare ADEAS with our current daily practice (conventional medication surveillance) as golden standard in the proof of principle test and in the study in **chapter 4**. In addition we compared ADEAS in a smaller setting with chart review in **chapter 5** because it is more labour intensive. In this study in **chapter 5** the comparison of a set of 16 clinical rules from ADEAS with manual pharmacist medication review revealed that a considerable proportion of the medication errors (dosing errors and therapeutic errors) detected by chart review are also detected by the clinical rules.

Following the results of the clinical validity studies we can conclude that ADEAS is able to detect patients at risk of ADEs and that this method is a useful addition to the conventional medication surveillance, a basic CDSS within our CPOE.

Clinical utility

The goal of ADEAS is to prevent harm and to enable clinical pharmacists to make corrective interventions guided by alerts from ADEAS. The extent in which ADEAS with clinical rules can actually prevent ADEs, the 'clinical utility', is investigated in **chapter 6**. This investigation showed that the use of ADEAS and subsequent interventions by the hospital pharmacist resulted in a 37% relative risk reduction for possible or definitely preventable ADEs. Other investigations also showed that the use of CPOE and CDSS can reduce ADEs [5-7]. In their review, Ammenwerth et al. described six studies with a 35% to 98% relative risk reduction for potential ADEs and four studies with a 30% to 84% relative risk reduction for ADEs. The CPOE/CDS systems in these studies varied between no CDSS (only CPOE), limited CDSS or advanced CDSS [5]. It is difficult to compare the effect of ADEAS with other investigations, because most studies investigating the effect of CPOE and CDSS on medication errors and ADEs differ substantially in their setting, type of system (home-grown or commercial), design, quality and consequently their results. Many studies, like ours, have the same limitations regarding for example the comparability between intervention and comparison group, no adjustment for confounding factors or use of lower level study designs and the chosen detection method for ADEs [5]. To partly resolve this problem, recently several guidelines for health informatics evaluation studies has been published, for example the STARE-II guidelines [33].

We have not investigated the isolated effect of ADEAS on prevention of ADEs, but we have investigated the effect of ADEAS combined with interventions by the hospital pharmacist. Two other investigations studying the effect of pharmacist intervention found a higher

reduction in preventable ADEs. Leape et al. found a 66% reduction in the ICU setting and Kucukarslan et al. found a 78% reduction in a general internal medicine unit [34,35]. In these two studies the pharmacist participated on ward rounds. Regarding the role of the hospital pharmacist, more studies have shown that participation of clinical pharmacist with healthcare teams on patient rounds indeed resulted in improved care and this method is also suggested as one of the methods to prevent ADEs [33,36,37]. Our intention was to encourage hospital pharmacist interventions focused on high risk patients, detected by our advanced CDSS using clinical rules. We did not participate on ward rounds because of limited capacity.

In three studies (**chapter 4, 6 and 7**) we reviewed the interventions made by the hospital pharmacist following alerts from ADEAS. In the prospective comparative study between ADEAS and the conventional medication surveillance (**chapter 4**), the hospital pharmacist made more interventions with a higher acceptance percentage following alerts from ADEAS compared to alerts from the conventional medication surveillance method. A limitation of this prospective study was that it was conducted on a small internal medicine ward. Consequently the absolute intervention and acceptance rate numbers were low. In **chapter 6 and 7** the absolute intervention numbers were considerably higher. The studies in these two chapters were conducted on five hospital wards. Our intervention percentage varied between 9% (**chapter 6**), 10% (**chapter 7**) and 19.4% (**chapter 4**). This percentage of safety alerts, resulting in an advice or intervention by the hospital pharmacist, may seem low, but is comparable or even higher than in other international investigations. Jha et al. investigated a commercial computerized surveillance system and found that in 11.3% reviewed alerts the physician was contacted [38]. Kilbridge et al. evaluated 4604 triggers from a computer-based ADE surveillance system with rules of which 4% led to an intervention [39]. The intervention percentages found by Silverman et al. with their computer-based monitoring system with rules ranged from 5 to 13% [26].

When we compare our intervention acceptance rates, 41% (**chapter 6**), 63% (**chapter 7**) and 71% (**chapter 4**), with acceptance rates found in other studies, our rates are lower. Two studies in which pharmacists gave dosages advices in case of impaired renal function showed an acceptance rate of 74% and 88% respectively [15,16]. In addition the study of Silverman et al. with his computer-based system reports an acceptance rate of 78.7%, 90.9% and 92.2% in their 3 different study periods [26]. When looking at studies regarding pharmacist participation on ward rounds, the before mentioned study of Leape et al. in the ICU found a 99% acceptance rate [35]. Similarly, the study of Kucukarslan et al. on a general medicine unit documented an acceptance rate of 98% [34]. An explanation could be that face-to-face contact leads to a higher intervention acceptance rate. In **chapter 6 and 7**

almost all interventions were made by phone, but in **chapter 4**, with a higher acceptance rate, most interventions were made by ward visit. Because of the small absolute numbers we cannot make solid conclusions at this point, but it is important not to underestimate ward visits, although they are more time-consuming in general. Thus by selecting patients at risk of potential ADEs, and making goal-oriented visits to the ward, the pharmacist can be more time-efficient than by routinely participating on ward rounds.

Future perspectives of ADEAS and clinical rules

In our three clinical utility studies (**chapter 4, 6 and 7**), we found that a relatively small number of the clinical rules active in the system ADEAS resulted in alerts. **Chapter 7** showed that the overall rule effectiveness and positive predictive value (PPV) of ADEAS is low (0.10 and 0.08 respectively). In **chapter 6** the overall rule effectiveness and PPV were 0.09 and 0.07 respectively. When we recalculate the number the same way for the prospective study in **chapter 4** we can estimate an overall rule PPV for ADEAS of 0.06. This means that 9-10% of the safety alerts generated with ADEAS resulted in a contact moment by the hospital pharmacist with the physician or nurse and that 6-8% of the alerts resulted in an advice or intervention to prevent a possible ADE. This does not automatically imply that most of the alerts are useless. These alerts can indeed indicate a potential ADE situation, but in specific patient cases the alert can be rated as 'non-relevant', after review and check of EPF in detail. The alert can therefore be considered useful as it does lead to a medication check by the pharmacist, but does not result in an intervention or contact moment. A few of such situations are explained in more detail in the discussion of **chapter 7**. All of these explained reasons are related to the low sensitivity or low specificity of several clinical rules in ADEAS. In some cases the clinical rules were adapted during the studies to increase their sensitivity or specificity. Adapting the content of the rules during use is an acceptable way to improve the PPV for the clinical rules [26]. To lower the number of 'non-relevant' alerts we aim to increase the rule effectiveness and PPV of ADEAS in the near future. One strategy is to add more sub items to a clinical rule. For example the sub item 'drug dosage' can be added in a rule regarding drug use and a declined renal function. Incorporating a cut-off dose under which no action is required and thus no alerts are generated can make the rules more efficient. In addition, the sub items 'ward' or 'specialty' can be added in a rule not relevant for a specific patient category. Some other investigators have already suggested a similar approach which underlines the importance and usefulness of such a strategy [40-42]. For example Scheidling et al. suggested to refine drug-drug interactions

with statin-drugs by using an upper dose limit [41]. In addition, Riedmann et al. searched for context factors, such as patient, prescriber/ward or alert characteristics, to prioritize drug-drug interactions [40]. Duplicate alerts are also a problem. These arise when the potential ADE situation keeps on existing, while for example already has been agreed on that the potential ADE situation is not harmful for this specific patient. Consequently a smart way to lower the number of duplicate alerts has to be created. A sub item looking at the previous generated alert with that clinical rule in the same patient might be added to the rule.

The rule effectiveness and PPV number between the categories of clinical rules was highly variable in our studies, a finding which is often observed in the literature. Kilbridge et al. reports a widely varied PPV for their rules, ranging from 0.00 to 0.67. The rule efficiency varies between 0.00 and 0.21. The highest PPV values are found for rules detecting ADEs (e.g. antidote order). Rules with evolving unsafe situations had lower PPV [39]. Comparable numbers for PPV are found in the study of Silverman et al.; their rule efficiency varied between 0.05 and 0.13. They suggested that a realistic goal is a rule efficiency of 0.10 and an idealistic goal a rule efficiency of 0.20 [26]. This indicates that our results can be considered promising.

In our investigations the combination of rule effectiveness and PPV was highest for clinical rules based upon the basic CPOE medication safety alerts fine-tuned to high risk patients (risk category 5, see for details **chapter 3 and 7**). Most consults and advices are given following alerts from clinical rules related to laboratory values (risk category 1 and 2, see for details **chapter 3 and 7**). These three risk categories together cover 95 clinical rules. The first step to adapt ADEAS in the near future can be to narrow our clinical rules set to these three risk categories. These rules are most promising to improve the performance of ADEAS and to optimize the benefit for routine patient care.

A limitation of our research is that we have not studied cost-effectiveness of the application ADEAS and the interventions of the hospital pharmacists. Time and cost aspects are obviously very relevant subjects for implementation novel methods for medication surveillance. It is our experience that developing, building, validating and supporting a system such as ADEAS is very time-consuming and very costly. Are all the time and money efforts in balance with the medication safety profit it brings us? We cannot give an answer to that important question with the studies in this thesis and this remains a challenging pharmaco-economic issue for future investigation.

ADEAS is developed as a pharmacy decision support system and not as a CDSS within the CPOE. The alerts generated by the system are noticed by the pharmacist and not by the

prescribing physician. The reason for this is that we believe that pre-screening of safety alerts by the pharmacist is useful to prevent alert fatigue with the physician [19,43]. In our studies we indeed see a large difference between the number of alerts compared to the number of intervention and advices. A review from Van der Sijs et al. described that in more than half of all cases, physicians ignore safety alerts. This can lead to error producing situations; the physician may not recognize a really clinical relevant and important alert in all cases [27]. Another study from Van der Sijs et al. indeed showed that safety alerts from a basic CDSS within a CPOE, similar as we use in our hospital, were frequently overridden [44]. Medication surveillance is the core business of the pharmacist, and it is suggested that the prescribers' knowledge of potential clinically relevant drug-drug interactions is limited in general [45]. Another argument to use ADEAS primarily as a pharmacy decision support system was that we wanted to use ADEAS as a tool for the hospital pharmacist for more clinical ward-based activities. This goal is not completely accomplished. Our ward-based activities have not substantially grown since the introduction of ADEAS. Thus for future perspective we have to find a way to enlarge clinical activities by use of ADEAS.

For the near future we suggest to distinguish three different objectives for our clinical rules:

1. *Clinical rules as daily medication safety alerts for the hospital pharmacist.*
   These are safety alerts that do not need immediate action by the physician and are pre-screened by the hospital pharmacist. These safety alerts can be generated in the hospital pharmacy daily. This way of using clinical rules was subject of research in this thesis.
2. *Clinical rules as daily medication safety alerts for the physician.*
   These are safety alerts that need immediate action by the physician. These safety alerts can be generated online while prescribing medication within the CPOE. For this goal ADEAS and our CPOE have to be integrated.
3. *Clinical rules that can be used as periodic medication review tool by the hospital pharmacist.*
   These are safety alerts that can be used for the review or screening of medication to optimize pharmacotherapy for example in long stay facilities, during weekly ward rounds, or at discharge. Also this can be safety alerts that focus on one specific issue e.g. costs or efficiency (for example all patients with three or more days of intravenous antibiotic therapy). These safety alerts can be generated on demand for one specific patient or one specific rule. These alerts are probably more suited for ward-based activities.

In this thesis we investigated our own developed and built ('home-grown') CDSS ADEAS, based on Gaston, and compared it only with one other basic CDSS within a CPOE (Medicator). The fact that these systems are not used in all hospitals in The Netherlands does not mean that our results are not relevant for a larger public. The concept of the clinical rules, validation issues, how to create better PPVs, is applicable for all (hospital) pharmacies in The Netherlands (and abroad) who have started or aim to start to use clinical rules. The use of clinical rules in Dutch hospital pharmacy practice is growing [46-50] and it is useful to share information and to learn from these practices. This thesis is one of the first reports that gives a total overview of experience with the development of a CDSS with clinical rules and its use in the hospital pharmacy setting.

Also on a national level the importance of clinical rules is recognized. The Dutch Hospital Pharmacists Association (Nederlandse Vereniging van Ziekenhuisapothekers, NVZA) has initiated a working group 'Clinical rules' which recently has published a starting document on how to use clinical rules and a start set of 10 different clinical rules (http://www.kennisplein-nvza.nl/thema_s/fpz/clinical_rules). Also the Royal Dutch National Pharmacists Association (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, KNMP) has initiated a multidisciplinary expert-group for clinical rules (expert-groep Medisch-Farmaceutische Beslisregels). The task of this group is to formulate clinical rules on specific topics for community pharmacists, general practitioners, hospital pharmacist and medical specialists in the hospital. In the future these clinical rules will be tested by the software companies of the different pharmacy information systems in The Netherlands, and thus will turn out to be standard for all pharmacies in the country. The future policy (2013-2017) of The Dutch Hospital Pharmacists Association focuses on pharmaceutical patient care throughout the entire stay of the patient within the hospital or care facility. Clinical rules are incorporated as a part of the practice of pharmaceutical care within this policy. Besides, the use of clinical rules within the hospital is a quality performance indicator within the Dutch program of Zichtbare Zorg (ZIZO) pharmacy.

Finally our future goals and activities regarding ADEAS and clinical rules will enhance the following subjects:

- To guarantee the quality and to secure the performance of ADEAS
- To integrate the two systems, ADEAS and the conventional medication surveillance, within one system
- To implement a method to ensure that the content of the clinical rules is always up-to-date

- To narrow the current set of clinical rules by focusing on three main risk categories:
  - Combination of biochemical laboratory values with the initiation of a drug
  - Combination of biochemical laboratory values or therapeutic drug monitoring values with the ongoing use of a drug
  - Basic CPOE medication safety alerts fine-tuned to high risk patients
- To enlarge rule effectiveness and PPV of the clinical rules
- To adapt our clinical rules to the three main targets:
  - Clinical rules as daily medication safety alerts for the hospital pharmacist
  - Clinical rules as daily medication safety alerts for the physician
  - Clinical rules that can be used as periodic medication review screening tool by the hospital pharmacist
- To define new clinical rules covering for example our special interest topic pharmacogenetics
- To enhance ward visits

Clinical rules will definitely remain and this thesis hopefully contributes to the optimal use of clinical rules in hospital pharmacy practice.

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Summary

Introduction

Drug use is common but in addition to positive effect it can also lead to unwanted effects. Adverse drug events (ADE) refer to any injury resulting from the use of a drug. ADEs can be due to a medication error or an adverse drug reaction (side effect of a drug). Medication errors can be prevented most of the time. Adverse drug reaction on the other hand cannot always be prevented.

ADEs occur frequently in hospitalized patients. A substantial proportion of these ADEs are considered preventable. These are mostly ADEs caused by a medication error. The literature describes different methods to prevent ADEs. For example barcoding of drugs and patients, intravenous admixture units for patient care and computerized physician order entry (CPOE) instead of handwritten paper recipes. Obviously, each method interacts in a particular part of the drug distribution chain, from prescribing, dispensing to drug use. In this thesis two methods are described, namely 1) CPOE with clinical decision support system (CDSS) and 2) clinical pharmacist activities.

At our institution, Leiden University Medical Center (LUMC), a CPOE with basic CDSS is in use since 2003. This CPOE system gives basic drug-drug interaction and drug dosing alerts to the physician while prescribing medication and can in that way prevent some medication errors and ADEs. This is called conventional medication surveillance. Our hypothesis is that the use of a more advanced CDSS incorporating clinical rules can improve the identification of patients at risk of ADEs. These clinical event-monitoring systems can use any data available in electronic form to detect potential ADEs and risk situations. The clinical rules or algorithms are based on identifiers which search for specific medication orders, patient characteristics and/or laboratory values. In addition, hospital pharmacists can interfere to prevent ADEs and, as such, improve medication safety. We have chosen to combine two strategies to prevent ADEs: CDSS for identifying patients at risk of ADEs and hospital pharmacist intervention focused on the specific patients at risk.

The aim of this thesis is 1) to develop a CDSS with clinical rules for use in the hospital pharmacy to identify patients with potential ADEs and 2) to investigate the ability of this system to identify these patients at risk of ADEs and finally 3) to investigate if these potential ADEs can be prevented by interventions by the hospital pharmacist. All of these studies focus on the hospitalized patient.

This thesis is divided in five parts. The first part, the introduction, starts with a comprehensive review of the literature in which an overview is presented of methods described to prevent

ADEs (**chapter 2**). In this review two strategies of prevention, pharmacist participation on ward rounds and CPOE with CDSS are highlighted. Moreover, two promising CDSS are discussed in more detail, namely computer-based monitoring systems and information systems which link laboratory and pharmacy data. The second part describes the development and the validity tests of our home-grown CDSS (analytical validity). In the third and fourth part of this thesis the clinical validity and clinical utility of the new system is discussed. The fifth part contains the general discussion and a future outlook.

Analytical validity

Chapter 3 describes the development and validation of the CDSS with clinical rules aimed to identify patients at risk of ADEs. The system is named Adverse Drug Event Alerting System (ADEAS). ADEAS is based on Gaston software (Medecs BV, Eindhoven, The Netherlands), which is a guideline-based decision support framework, consisting of both a guideline development module and a decision support module. The guideline development module describes the structure (flow) of the guideline by means of knowledge or data available in electronic form, such as data on drug prescription, laboratory values, patient characteristics and drug-drug interactions. The decision support module was used to link Gaston with our hospital information system, CPOE and the Dutch drug information database G-Standard (Z-Index, The Netherlands) in order to import the required information and to execute the clinical rules. The content of the clinical rules was defined with the help of a multidisciplinary team. From a drug perspective seven risk categories were identified, which were used to create the clinical rules:

1. Combination of biochemical laboratory values with the initiation of a drug
   example: patient starts with vancomycin and renal function is not known
2. Combination of biochemical laboratory values or therapeutic drug monitoring values with the ongoing use of a drug
   example: patient uses gentamycin and no therapeutic drug monitoring
3. Combination of the use of a drug with the non-use of another drug, intended to prevent an ADE
   example: patient with chronic use of opioid receptor agonist and no prescription of laxative
4. Medication used to treat an ADE

5. Basic CPOE medication safety alerts fine-tuned to high risk patients *example: patient (> 60 yr) with NSAID prescription but no prescription of proton pump inhibitor for protection of stomach ulcer*
6. Safety alerts from inspection authority or drug companies
7. Medication errors and high risk drug situations

A total of 121 clinical rules with a wide clinical coverage were built into the system. After building the clinical rules into ADEAS, we performed a technical validation of the system. A technical validation is necessary to establish whether the system works according to the specification and our expectations. A validation program was developed and written, because there are no existing guidelines for validation of a CDSS such as ADEAS. We choose three different methods for the validation of ADEAS: 1) by use of dummy patients in the CPOE, 2) testing ADEAS in an off-line test setting, and 3) behind-the-scene testing of ADEAS and manual check of the results with the electronic patient file (EPF).

The development and validation of ADEAS was time-consuming but eventually we managed to successfully develop a CDSS for us in the hospital pharmacy.

Clinical validity

To investigate the ability of ADEAS to identify patients at risk of ADEs we have compared ADEAS with other ADE detection methods. First in **chapter 3** we have performed a proof of principle test. In this study we retrospectively compared the alerts of a set of 13 clinical rules in ADEAS with the alerts from our conventional medication surveillance during a 3-day period. The conventional medication surveillance consists of basic CDSS alerts (drug-dosing alerts and drug-drug interaction alerts) that are visible online for the physician while ordering medication within the CPOE. The proof of principle test showed that ADEAS is potentially useful and is complimentary to the conventional system. ADEAS generated alerts and detected additional risk situations, which were not generated by conventional medication surveillance.

Chapter 4 describes a retrospective and a prospective comparison of ADEAS with the conventional medication surveillance. In these two studies all 121 clinical rules in ADEAS were active. The retrospective comparison of ADEAS was conducted on all patients admitted to the hospital (except patients admitted on intensive care unit) during a 1-month period. ADEAS generated in this period 2010 alerts, compared to 2322 alerts generated by the

conventional medication surveillance method. The prospective comparison between the new ADEAS system and the old medication surveillance system was performed during a 6-month period. All patients admitted to one general internal medicine ward were included. Every day ADEAS searched for risk situations in the EPF of the patients and generated alerts. Following the alerts the hospital pharmacist could give advice to the physician or nurse to prevent a detected potential ADE. The alerts from both systems were compared daily. ADEAS generated 248 alerts during the 6-month study period whereas the conventional medication surveillance generated 177 alerts. Following the alerts from ADEAS the hospital pharmacist made 14 interventions compared to 5 interventions following the alerts from the conventional system. The type of risk patient identified by ADEAS was different compared to the conventional medication surveillance. The conventional medication surveillance generated safety alerts regarding drug-drug interactions and drug overdosing. ADEAS generated alerts regarding a declined renal function and the use of medication, which needed dose reduction, and the absence of essential concurrent medication.

In **chapter 5** the results of ADEAS are compared with manual medication review by a pharmacist. Manual chart review is a well-known method to search for ADEs. The alerts from ADEAS, with 16 clinical rules active, were compared with therapeutic medication errors found by manual chart review. ADEAS detected 39% of the medication errors found with chart review. A combination of ADEAS together with conventional medication surveillance, a basic CDSS within a CPOE, detected 66% of the medication errors.

Following the results of the clinical validity studies we can conclude that ADEAS is able to identify patients at risk of ADEs and that this method is a useful addition to the conventional medication surveillance.

Clinical utility

The goal of ADEAS is to prevent harm and to enable hospital pharmacists to make corrective interventions guided by alerts from ADEAS.

Chapter 6 describes the investigation of the extent to which ADEAS based interventions by hospital pharmacists can prevent ADEs in the elderly patient (> 65 years of age) with polypharmacy (> 5 drugs). Before implementation of ADEAS only conventional medication surveillance was present. After implementation of ADEAS both methods were used to select risk situations. ADEAS was run every night and the following morning hospital pharmacists collected all generated alerts. Subsequently additional case specific information for each

patient was collected by the hospital pharmacist. If necessary the hospital pharmacist made an intervention to prevent the potential ADE. The number of ADEs was compared before and after the introduction of ADEAS. Retrospectively all charts of the included patients were searched for ADEs by manual chart review. The detected ADEs were subdivided in preventable and not preventable ADEs. In the period before use of ADEAS 42 preventable ADE were found by manual chart review in 240 hospital admissions. After implementation of ADEAS 27 preventable ADEs were found in 248 hospital admissions. We calculated a relative risk reduction of 37%. Many studies that investigate ADEs, ours included, have limitations regarding for example the comparability of the intervention and comparison group, the design of the study, possible confounding factors and the selected detection method for ADEs. But overall we can conclude that ADEAS based interventions by the hospital pharmacist can reduce the number of ADEs compared to the use of conventional medication surveillance alone.

In **chapter 7** we describe our experience with the daily use of ADEAS in hospital pharmacy practice. In addition to the evaluation of the ADEAS system, also the assessment of the rule effectiveness and the positive predictive value (PPV) of the clinical rules was studied. During the 5-month study period ADEAS generated 2650 safety alerts in a total of 931 patients admitted to the hospital. In 270 alerts (10%) the hospital pharmacist contacted the physician or nurse and in 204 cases this led to an advice to prevent a possible ADE. A measure of rule effectiveness is the ratio of the number of alerts resulting in contact with the healthcare professional to the total number of alerts generated by ADEAS. The overall rule effectiveness was 0.10. The PPV was calculated from the quotient of the number of interventions to prevent a possible ADE and the total number of alerts generated by ADEAS. The overall PPV was 0.08. Most alerts were generated with clinical rules from the categories linking pharmacy and laboratory data (risk category 1 and 2). Combination of rule effectiveness and PPV was highest for clinical rules based upon risk category 'basic CPOE medication safety alerts fine-tuned to high risk patients'. In that case rule effectiveness was 0.17 and the PPV was 0.14.

The conclusion of the results in **chapter 7** is that ADEAS can effectively be used in daily hospital pharmacy practice to identify patients at risk of potential ADEs, but to increase the benefits for routine patient care and to increase efficiency, both rule effectiveness and PPV for the clinical rules should be improved.

General discussion

In the last part of this thesis, **chapter 8**, the development of ADEAS and the clinical rules, the ability of the system to identify patients at risk of potential ADEs and to prevent these ADEs is discussed and put in perspective. This chapter also describes our ideas for future use of clinical rules in hospital (pharmacy) practice to identify risk patients, to prevent ADEs and ultimately to make drug use safer for our patients.

Summarizing, the development of ADEAS was successful, but it would have been a better strategy to start with a smaller set of clinical rules instead of our comprehensive set with a wide clinical coverage. An alternative strategy would be to start with the most effective clinical rules, those belonging to risk category 1, 2 and 5. With a smaller set of clinical rules the development and validation process would have been less time-consuming.

A strong aspect of ADEAS is that it combines data from different databases available in the hospital information system. In particular the use of laboratory data is of added value in clinical rules. Also the absence of essential concurrent medication can be found through ADEAS. This is in contrast to the conventional medication surveillance, which cannot detect these situations. Examples of useful safety alerts based on clinical rules are: 1) patient with vancomycine therapy and absence of blood monitoring for vancomycine concentration, 2) too high a dose of a drug in a patient who suffers from a declined renal function and 3) patient with chronic opioid use and no laxative therapy. ADEAS generates alerts in evolving unsafe situations and can in this way help to prevent harm from an ADE. This is in contrast with older computerized alert systems that generate an alert for example when the physician prescribes an antidote. But in that case harm already has occurred and consequently cannot be prevented anymore.

For future use our goal is to improve rule effectiveness and positive predictive value. At this moment ADEAS generates too many false positive alerts; alerts that do not require any action. For example ADEAS generates an alert when a patient has a declined renal function and uses ciprofloxacin. The hospital pharmacist checks the dose of the drug in the CPOE and concludes that the physician correctly adapted the dose to the declined renal function. This kind of safety alert does not lead to an intervention by the hospital pharmacist, but is still a useful alert. In the future the clinical rules can be optimized by adding a sub item regarding the dose of the drug, so it becomes more clinical relevant. For now ADEAS is used in the hospital pharmacy. In the future we would like to integrate ADEAS within our CPOE, so safety alerts can also be generated real-time online for the prescribing physician. Before this can be realized the percentages of false positive alerts must be acceptably low. If the

percentage of false positive alerts is too high there is a risk of alert fatigue. This means that the physician can miss a real import safety alert with the possible consequence of patient harm. For the future we suggest distinguishing three different objectives for our clinical rules:

1. Clinical rules as daily medication safety alerts for the hospital pharmacist
2. Clinical rules as daily medication safety alerts for the physician
3. Clinical rules that can be used as periodic medication review tool by the hospital pharmacist

Our future goals and activities regarding ADEAS and clinical rules will focus on the integration of the two systems ADEAS and the conventional medication surveillance. We should guarantee the quality and secure the performance of ADEAS. And we must not forget our clinical pharmacy activities, thus another future goal is to enhance ward visits.

In this thesis we have investigated our self-developed and built home-grown CDSS ADEAS. LUMC is one of the first hospital pharmacies who have adopted the concept of clinical rules. This thesis can contribute to optimal use of clinical rules in hospital pharmacy practice. Both The Dutch Hospital Pharmacists Association (Nederlandse Vereniging van Ziekenhuisapothekers, NVZA) and the Royal Dutch National Pharmacists Association (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, KNMP) support the importance of the use of clinical rules. Clinical rules will definitely remain and will contribute to optimal use of medication and enhance medication safety.

Samenvatting

Inleiding

Geneesmiddelen worden veel gebruikt voor het bestrijden of voorkomen van ziektes en symptomen, maar naast het gewenste effect kunnen geneesmiddelen ook tot schade leiden. Deze neveneffecten door het gebruik van geneesmiddelen worden in het Engels 'adverse drug events' (ADEs) genoemd. ADEs kunnen worden veroorzaakt door de werking van het geneesmiddel zelf, dit wordt bijwerking genoemd, of door het foutief gebruik van het geneesmiddel, ook wel medicatiefout genoemd. Medicatiefouten kunnen vaak voorkomen worden; bijwerkingen niet altijd.

ADEs treden regelmatig op bij patiënten die opgenomen zijn in het ziekenhuis. Een deel van deze ADEs wordt als vermijdbaar beschouwd. Dit zijn met name ADEs veroorzaakt door medicatiefouten. Er zijn verschillende methoden in de wetenschappelijke literatuur beschreven waarmee ADEs mogelijk verminderd of voorkomen kunnen worden. Voorbeelden zijn o.a. barcode scannen van geneesmiddelen en patiënten, speciale bereidingsunits op de verpleegafdeling voor het voor toediening gereed maken van intraveneus toe te dienen geneesmiddelen en het voorschrijven van geneesmiddelen via een elektronisch voorschrijf systeem (EVS) in plaats van op een handgeschreven papieren recept. Elke methode heeft invloed op een deel van het geneesmiddeldistributieproces, van voorschrijven, leveren en klaarmaken tot toedienen. In dit proefschrift komen 2 methodes aan bod, namelijk 1) het gebruik van een klinisch beslissingsondersteunend computersysteem als toevoeging aan het EVS voor medicatie in het ziekenhuis en 2) interventies door de ziekenhuisapotheker.

In het Leids Universitair Medisch Centrum (LUMC) wordt bij het voorschrijven van geneesmiddelen gebruik gemaakt van een EVS. Tijdens het elektronisch voorschrijven van geneesmiddelen krijgt de arts automatisch meldingen met betrekking tot overdoseringen en geneesmiddelinteracties te zien. Deze standaard medicatiebewaking kan al een aantal ADEs voorkomen. Wij denken dat een meer geavanceerde medicatiebewaking door middel van het gebruik van een klinisch beslissingsondersteunend computersysteem een toegevoegde waarde heeft om nog meer ADEs te voorkomen. Zo'n systeem maakt gebruik van medisch farmaceutische beslisregels, in het Engels 'clinical rules' genaamd. Dit zijn vooraf gedefinieerde algoritmes gebaseerd op een combinatie van gegevens uit het elektronisch patiëntendossier, zoals geneesmiddelgebruik, (klinisch-chemische) laboratoriumwaarden en patiëntkarakteristieken. Met behulp van deze clinical rules worden patiënten met een mogelijk risico op een ADE opgespoord. Vervolgens kan de ziekenhuisapotheker contact opnemen met de arts of de verpleging om een advies te geven en zo mogelijke ADEs helpen voorkomen.

Het doel van dit proefschrift is om 1) een klinisch beslissingsondersteunend systeem te ontwikkelen voor gebruik in de ziekenhuisapotheek om patiënten met een risico op een ADE op te sporen, vervolgens 2) te onderzoeken of dit systeem ook daadwerkelijk relevante risicopatiënten opspoort en 3) te onderzoeken of de mogelijke ADEs die opgespoord worden door het systeem ook voorkomen kunnen worden door interventies door de ziekenhuisapotheker.

Dit proefschrift bestaat uit vijf delen. Het eerste deel, de introductie, omvat een algemene inleiding in **hoofdstuk 1** en een uitgebreid literatuuronderzoek in **hoofdstuk 2** waarin diverse methodes om ADEs te voorkomen worden beschreven. In het literatuuronderzoek wordt ingezoomd op klinisch beslissingsondersteunende computersystemen met clinical rules als methode om ADEs te voorkomen en dan met name de connectie tussen geneesmiddelgebruik en de laboratoriumwaarden van de patiënt. Het tweede deel beschrijft de ontwikkeling en validatie van ons eigen klinisch beslissingsondersteunend systeem (analytische validiteit). Het derde en vierde deel van dit proefschrift bevatten respectievelijk onderzoeken naar de klinische validiteit en de klinische toepasbaarheid van het nieuwe systeem. Het vijfde deel bevat een discussie van het in het proefschrift beschreven werk en een beschouwing van toekomstige ontwikkelingen.

Analytical validity

Hoofdstuk 3 beschrijft de ontwikkeling en validatie van ons eigen klinisch beslissingsondersteunend systeem, genaamd 'Adverse Drug Event Alerting System' (ADEAS). ADEAS is samengesteld in Gaston software (Medecs BV, Eindhoven). Gaston bestaat uit een richtlijneditor waarin de clinical rules kunnen worden samengesteld en een beslissingsondersteunende module die communiceert met de diverse elektronische informatiesystemen en de beslisregel vertaalt in door de computer uit te voeren stappen. De systemen waaruit informatie wordt opgehaald zijn: geneesmiddelvoorschrijfgegevens uit het EVS, klinisch-chemische laboratoriumwaarden en patiëntenkarakteristieken uit het elektronisch patiëntendossier en geneesmiddelengegevens en interacties uit de G-Standaard (Z-Index, Nederlandse geneesmiddeldatabase). De clinical rules zijn geformuleerd in een multidisciplinair team op basis van zeven risicocategorieën:

1. Laboratoriumwaarden van de patiënt gekoppeld aan de start van een geneesmiddel
   voorbeeld: patiënt start met vancomycine zonder dat de nierfunctie bekend is

2. Laboratoriumwaarden van de patiënt gekoppeld aan het gebruik van een geneesmiddel
   voorbeeld: patiënt gebruikt gentamicine zonder dat de bloedspiegels gecontroleerd worden
3. Ontbreken van relevante beschermende comedicatie
   voorbeeld: patiënt gebruikt chronisch opiaat pijnstiller zonder laxans
4. Geneesmiddel in gebruik voor de behandeling van een bijwerking van een ander geneesmiddel
5. Standaard geneesmiddelinteracties uit het EVS aangepast aan risicopatiënten
   voorbeeld: patiënt ouder dan 60 jaar met NSAID pijnstiller zonder maagbescherming
6. Veiligheidssignalen van de inspectie en geneesmiddelenleveranciers
7. Veel voorkomende medicatiefouten en risicosituaties

In totaal zijn er 121 clinical rules geformuleerd met een brede farmacotherapeutische omvang. ADEAS is vervolgens gevalideerd om te controleren of het systeem de situatie beschreven in de clinical rule correct detecteert. Met andere woorden of het systeem geen vals positieve of vals negatieve signalen genereert. Er was geen standaard validatieprogramma beschikbaar, waardoor we zelf een validatieprogramma hebben ontwikkeld. De validatie is uitgevoerd op drie manieren: 1) door gebruik te maken van dummypatiënten in het EVS, 2) door ADEAS te testen in een offline testomgeving, en 3) door ADEAS achter de schermen te laten draaien en de signalen handmatig te controleren met de klinische gegevens van de patiënten.

De ontwikkeling en validatie hebben veel tijd in beslag genomen maar uiteindelijk is het gelukt om ADEAS te ontwikkelen als klinisch beslissingsondersteunend systeem voor de ziekenhuisapotheek.

Klinische validiteit

Om te onderzoeken of ADEAS ook daadwerkelijk relevante risicosituaties, dus patiënten met een risico op een ADE opspoort, is ADEAS vergeleken met andere methodes om patiënten met een ADE op te sporen. In **hoofdstuk 3** is eerst een proof-of-principle test uitgevoerd. In dit onderzoek zijn 13 clinical rules in ADEAS aangezet en zijn gedurende drie dagen de veiligheidssignalen die door ADEAS werden gegenereerd verzameld bij alle in het ziekenhuis opgenomen patiënten. De resultaten zijn retrospectief vergeleken met de

signalen die de arts ziet tijdens het voorschrijven van medicatie afkomstig van de standaard medicatiebewaking in het EVS gedurende dezelfde periode. Hieruit bleek dat met ADEAS additionele patiënten met een risico op een ADE werden gedetecteerd.

In **hoofdstuk 4** is ADEAS opnieuw vergeleken met de standaard medicatiebewaking in het EVS in twee onderzoeken, een retrospectieve en een prospectieve vergelijking. In het retrospectieve onderzoek werden alle 121 clinical rules in ADEAS geactiveerd en draaide het systeem gedurende één maand op alle patiënten opgenomen in het ziekenhuis (behalve de patiënten op de Intensive Care). ADEAS genereerde in die periode 2010 signalen. De standaard medicatiebewaking genereerde in dezelfde periode 2322 signalen. Voor het prospectieve onderzoek haalde ADEAS alleen gegevens op van de patiënten die waren opgenomen op een algemene interne geneeskunde afdeling. Dit onderzoek werd gedurende zes maanden uitgevoerd. De signalen werden dagelijks vergeleken met de signalen afkomstig van de standaard medicatiebewaking. Daarnaast gaf de ziekenhuisapotheker ook adviezen aan de arts of verpleging in navolging op een signaal. ADEAS genereerde gedurende deze zes maanden 248 signalen tegenover 177 signalen met de standaard medicatiebewaking. Veertien keer werd er door de ziekenhuisapotheker een interventie gedaan in navolging op een signaal vanuit ADEAS en vijf keer naar aanleiding van een signaal afkomstig van de standaard medicatiebewaking. Het soort mogelijke ADE dat met ADEAS bij patiënten wordt gedetecteerd is anders dan het soort mogelijke ADE wat wordt gedetecteerd met de standaard medicatiebewaking. De standaard medicatiebewaking geeft signalen bij overdoseringen en geneesmiddelinteracties. ADEAS geeft vooral signalen bij patiënten met een verminderde nierfunctie die een geneesmiddel gebruiken waarvan de dosis afhankelijk is van de nierfunctie en bij afwezigheid van noodzakelijke comedicatie.

In het onderzoek dat wordt beschreven in **hoofdstuk 5** is de werking van ADEAS vergeleken met handmatige medicatiebeoordeling door statusonderzoek. Deze laatste methode is een veel gebruikte manier om ADEs op te sporen. Zestien clinical rules in ADEAS werden geactiveerd en de signalen vanuit ADEAS werden vergeleken middels handmatig statusonderzoek met de gevonden medicatiefouten (o.a. overdoseringen en geneesmiddelinteracties). ADEAS detecteerde 39% van de therapeutische medicatiefouten. Wanneer standaard medicatiebewaking in het EVS en ADEAS werden gecombineerd werd 66% van de overdoseringen en therapeutische medicatiefouten gedetecteerd.

De resultaten van de onderzoeken met betrekking tot de klinische validiteit laten zien dat ADEAS in staat is relevante patiënten met een risicosituatie op te sporen en dat ADEAS ten opzichte van de standaard medicatiebewaking in het EVS additionele patiënten met een mogelijk risico op een ADE detecteert.

Klinische toepasbaarheid

Het uiteindelijke doel van de ontwikkeling van ADEAS is medicatieveiligheid en voorkomen van ADEs en schade door geneesmiddelengebruik bij de patiënt. In hoeverre medicatiebewaking met ADEAS gevolgd door interventies door de ziekenhuisapotheker ADEs kan voorkomen of verminderen wordt beschreven in **hoofdstuk 6** en **hoofdstuk 7**.

Hoofdstuk 6 beschrijft een onderzoek waarin voor en na de implementatie van ADEAS het aantal ADEs wordt onderzocht door middel van statusonderzoek bij de oudere in het ziekenhuis opgenomen patiënt (> 65 jaar) met polyfarmacie (> 5 geneesmiddelen). Voor de implementatie van ADEAS werd alleen gebruik gemaakt van medicatiebewaking in het EVS. Na de implementatie van ADEAS werden beide systemen gecombineerd; ADEAS en standaard medicatiebewaking. Het ADEAS-systeem draaide elke ochtend en genereerde signalen in de ziekenhuisapotheek. Vervolgens bekeek de ziekenhuisapotheker deze signalen en zocht relevante informatie op over de patiënt in het elektronisch patiëntendossier en gaf indien nodig advies aan de arts of verpleging om een mogelijke ADE te voorkomen. Retrospectief werden de statussen van de geïncludeerde patiënten handmatig nagezocht op ADEs. De gevonden ADEs werden onderverdeeld in potentieel wel of niet vermijdbaar. In de periode voor gebruik van ADEAS werden er middels statusonderzoek 42 vermijdbare ADEs gevonden in een groep van 240 patiëntenopnames en na de in gebruik name van ADEAS werden er middels statusonderzoek nog 27 vermijdbare ADEs in een groep van 248 patiëntenopnames gevonden. Dit betekent een relatieve risicoreductie van 37%. Zoals elk onderzoek heeft ook dit onderzoek zijn beperkingen. Bij onderzoek naar ADEs worden er altijd kritische vragen gesteld over de opzet van het onderzoek, de vergelijkbaarheid van de twee groepen patiënten, eventuele bias en de validiteit van de detectiemethode. Desondanks laat dit onderzoek zien dat met ADEAS gestuurde interventies door de ziekenhuisapotheker een reductie in ADEs kan worden bewerkstelligd ten opzichte van het gebruik van alleen medicatiebewaking in het EVS.

Hoofdstuk 7 beschrijft de ervaringen met het dagelijks gebruik van ADEAS in de ziekenhuisapotheek en geeft een berekening van de effectiviteit en de positief voorspellende waarde van de clinical rules. Gedurende vijf maanden genereerde ADEAS 2650 signalen bij totaal 931 in het ziekenhuis opgenomen patiënten. Bij 270 signalen (10%) nam de ziekenhuisapotheker contact op met de arts of verpleging en bij 204 signalen gaf de ziekenhuisapotheker daadwerkelijk een advies om een ADE te voorkomen. De effectiviteit van de clinical rules is berekend door het aantal signalen wat heeft geleid tot een overleg met de arts of verpleging te delen door het totaal aantal signalen. Dit resulteerde in een waarde van 0,10. De positief voorspellende waarde van de clinical rules is berekend door het aantal signalen wat heeft

geleid tot een advies te delen door het totaal aantal signalen. Dit resulteerde in een waarde van 0,08. De meeste signalen werden gegeneerd door clinical rules behorende tot de twee risicocategorieën betreffende de combinatie van geneesmiddel en laboratoriumwaarde van de patiënt (risicocategorie 1 en 2). De clinical rule effectiviteit en positief voorspellende waarde waren het grootst voor clinical rules behorende tot de risicocategorie 5 'standaard geneesmiddelinteracties uit het EVS aangepast aan risicopatiënten'. Deze beslisregels hadden een effectiviteitwaarde van 0,17 en een positief voorspellende waarde van 0,14.

Uit het onderzoek beschreven in **hoofdstuk 7** kan geconcludeerd worden dat ADEAS goed gebruikt kan worden in de dagelijkse praktijk van de ziekenhuisapotheek, maar dat de inhoud van de clinical rules moet worden geoptimaliseerd zodat de effectiviteitwaarde en positief voorspellende waarde verhoogd kunnen worden.

Algemene discussie

In het laatste deel, in **hoofdstuk 8**, worden de resultaten van het in dit proefschrift beschreven onderzoek kritisch besproken en wordt een toekomstvisie over het gebruik van clinical rules in de ziekenhuisapotheek gepresenteerd.

De ontwikkeling van ADEAS is succesvol, maar achteraf kan geconcludeerd worden dat de uitgebreide set beslisregels met een brede farmacotherapeutische dekkingsgraad niet de beste manier was om te beginnen. Een kleinere set clinical rules beperkt tot de risicocategorieën 1, 2 en 5 zou beter geweest zijn, omdat deze clinical rules het meest effectief zijn en met een beperkte set beslisregels het validatieproces minder tijdrovend was geweest.

De meerwaarde van ADEAS komt vooral tot uiting in de mogelijkheid om ook de laboratoriumwaarden te betrekken bij het opsporen van patiënten met een mogelijke ADE. Dit is niet mogelijk met de standaard medicatiebewaking in het EVS. Daarnaast houdt ADEAS ook rekening met de comedicatie van de patiënt, iets wat de standaard medicatiebewaking niet kan doen. Voorbeelden van nuttige veiligheidssignalen die werden gegenereerd aan de hand van clinical rules zijn: 1) het vergeten van laboratoriumcontrole van de vancomycineconcentratie in het bloed bij het gebruik van vancomycine, 2) een te hoge dosis van een geneesmiddel bij een patiënt met een verminderde nierfunctie en 3) het ontbreken van een laxans bij langdurig opiaatgebruik. ADEAS geeft signalen bij dergelijke risicosituaties en kan zo bijdragen schade bij de patiënt te voorkomen. Dit in tegenstelling tot computersystemen die pas signalen geven als de patiënt al schade heeft ondervonden, bijvoorbeeld bij het voorschrijven van een antidotum om de effecten van een overdosering tegen te gaan.

Voor toekomstig gebruik is het belangrijk dat de effectiviteit en positief voorspellende waarde van de clinical rules wordt geoptimaliseerd. Op dit moment zijn er nog te veel signalen waarbij uiteindelijk geen actie nodig is. ADEAS genereert bijvoorbeeld een signaal bij de risicosituatie ciprofloxacinegebruik bij een verminderde nierfunctie. De ziekenhuisapotheker controleert de dosering, maar er is geen actie nodig, want de arts heeft de dosering correct aangepast. Zo'n signaal leidt dus uiteindelijk niet tot een interventie. In de toekomst kan de clinical rule geoptimaliseerd worden door het item dosering toe te voegen als selectiecriterium in de beslisregel.

Op dit moment wordt ADEAS alleen gebruikt in de ziekenhuisapotheek. Als in de toekomst de signalen uit ADEAS rechtsreeks bij de arts terecht komen is het belangrijk dat het percentage niet klinisch relevante signalen laag is, want anders bestaat het risico op signaalmoeheid. Dat betekent dat er te veel onnodige veiligheidssignalen aan de arts getoond worden en de signalen niet meer gelezen worden met de consequentie dat de wel relevante signalen ook gemist worden. In de toekomst zien wij drie verschillende mogelijke toepassingen voor clinical rules:

1. Beslisregels als dagelijkse medicatiebewaking voor de ziekenhuisapotheker.
2. Beslisregels als dagelijkse medicatiebewaking direct tijdens het voorschrijven zichtbaar in het EVS voor de arts. Deze clinical rules selecteren risicosituaties waarbij direct actie nodig is en geen vertraging gewenst is.
3. Beslisregels die gebruikt kunnen worden voor een periodieke medicatiereview door de ziekenhuisapotheker.

Daarnaast moeten we energie steken in het integreren van ADEAS en de standaard medicatiebewaking, op dit moment nog twee afzonderlijke systemen. Verder vergt de borging van de kwaliteit van ADEAS en het up-to-date houden van het systeem onze aandacht. En niet te vergeten de klinische activiteiten van de ziekenhuisapotheker op de verpleegafdeling; deze moeten in de toekomst vergroot worden.

ADEAS is een eigen ontwikkeld klinisch beslissingsondersteunend systeem voor de ziekenhuisapotheek. Het LUMC is een van de eerste ziekenhuizen die dit concept heeft toegepast. Dit proefschrift kan bijdragen aan een verder optimaal gebruik van clinical rules in de Nederlandse ziekenhuisfarmacie. Zowel binnen de Nederlandse Vereniging van Ziekenhuisapothekers (NVZA) en de Koninklijke Nederlandse Maatschappij ter bevordering van de Pharmacie (KNMP) wordt het belang van het gebruik van clinical rules onderschreven. In de toekomst zijn clinical rules niet weg te denken uit de praktijk van de ziekenhuisapotheek en zullen zij bijdragen aan een optimaal gebruik van geneesmiddelen en het bevorderen van medicatieveiligheid.

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CV

Mirjam Kristien Rommers was born in Eindhoven, The Netherlands on September 10th 1974. After finishing secondary school (VWO) at the Sint Joris College in Eindhoven in 1992, she started her study Pharmacy at Utrecht University. In 1997 she obtained her doctoral exam, followed by her PharmD exam in 1999. As part of her doctoral program she worked for six months on a research project investigating the effect of modulators of arachidonc acid metabolism on breast cancer and stromal cells growth and function (supervisors Prof. dr. J.J.H. Thijssen, Dr. M.P. Schrey). This work was performed at St. Mary's Hospital in London, United Kingdom.

From June 1999 to December 2000, she worked as a pharmacist in the Hospital Pharmacy of Erasmus University Medical Center (supervisor Prof. dr. A. Vulto) in Rotterdam. In December 2000 she started her training as a hospital pharmacist, first two years in Hospital Pharmacy Midden-Brabant (ZAMB) (supervisor A.W. Lenderink) in Tilburg and after that two years in Hospital Pharmacy of Amphia Hospital (supervisor A. Schuurman) in Breda. As part of this training she performed a research project on the effect of subcutaneous oedema on the subcutaneous absorption of low molecular weight heparins in intensive care patients (supervisors Dr. P.L.M.A van der Bemt, Prof. dr. A.C.G. Egberts, Dr. N. van der Lely).

After finishing her training in December 2004 she started working as a hospital pharmacist in the section pharmaceutical patient care of the Department of Clinical Pharmacy & Toxicology of the Leiden University Medical Center (LUMC). At the same time she started working on the development of the clinical decision support system ADEAS and the studies presented in this PhD thesis (supervisors Prof. dr. H-J. Guchelaar, Dr. I.M. Teepe-Twiss). Her interests are, besides medication safety and pharmaceutical patient care, intensive care medicine and infectious diseases. She is secretary of the antibiotic committee of LUMC and member of the Special Interest Group Anesthesiology and Intensive care and working group clinical rules of the Dutch Hospital Pharmacists Association (NVZA) and member of the expert group clinical rules ('expert groep MFB') of the Royal Dutch National Pharmacists Association (KNMP). After completion of this PhD project she will continue her career as clinical hospital pharmacist in the field of pharmaceutical patient care at the Leiden University Medical Center.

Mirjam Rommers lives in The Hague and is married to Martijn Soesbeek. Together they have two children, Mees (2010) and Saar (2013).

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