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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.