Contextualized clinical decision support to detect and prevent adverse drug events

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Arthur Wasylewicz

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1

INTRODUCTION

CHAPTER 1.1

General introduction

GENERAL INTRODUCTION

ADVERSE DRUG EVENTS

One of the primary responsibilities of physicians, pharmacists, and other healthcare professionals is to prevent harm to a patient: Primum non nocere.[2] However, numerous studies have demonstrated that healthcare professionals are still unsuccessful in doing so.[3,4] Adverse events (AEs) are among the ten leading causes of death and disability worldwide.[5] They are defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment." In high-income countries, one in ten patients is harmed while hospitalized,[6] and nearly half of these occurrences are preventable.[7] Numbers are higher in low and middle-income countries,[4,8] resulting in 2.6 million deaths annually.[4] Adverse drug events (ADEs) are estimated to account for 19% of all adverse events.[9]

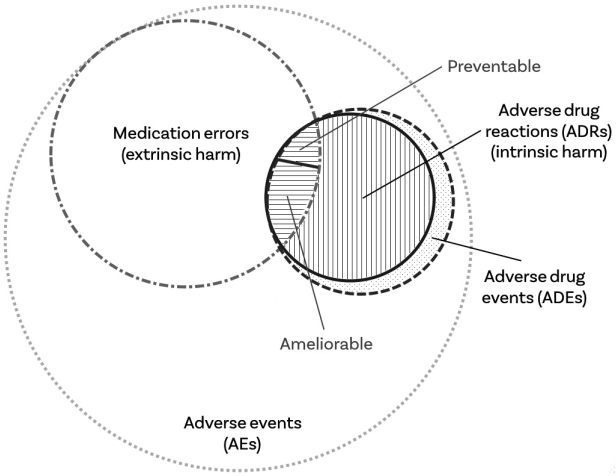

FIGURE 1. *Venn diagram illustrating the relationships between adverse events (circle with dotted line), medication errors (circle with dotted and dashed line), adverse drug events (circle with dashed line) and adverse drug reactions (circle with continuous line). Adopted and redacted from Morimoto et al., 2004.*[1]

ADVERSE DRUG EVENTS

An ADE (dotted and striped circle with dashed line in figure 1) is any injury occurring during the use of a drug. It can be the result of a pharmacological or immunological adverse drug reaction (ADR) (intrinsic harm) (vertically striped circle segment, figure 1), unassociated with the use of the drug (dotted section, figure 1), or associated with a medication error (extrinsic harm) (horizontally striped circle segment, figure 1).[1] Medication errors can occur at any stage of the medication use process, from therapy choice until monitoring of therapy.[10] Approximately 50% of ADEs are believed to be preventable[10] (preventable ADEs), and for

a larger percentage, the risk or severity of harm could have been reduced (ameliorable ADEs).[11] Figure 1 illustrates the relationship between the different terms. Dutch numbers are comparable to those in US, UK, and European studies.[12] Implementing electronic health records (EHRs) integrating computerized physician order entry (CPOE) and clinical decision support (CDS) systems is considered one of the key interventions to lower the number of ADEs associated with medication errors.[13,14]

CLINICAL DECISION SUPPORT SYSTEMS

Since the report "To Err is Human" was released, billions have been spent implementing EHRs, often with integrated CPOE and basic CDS systems.[15] Despite these efforts, however, high rates of ADEs persist.[16,17] Many types of medication errors disappeared with the implementation of CPOEs with integrated CDS systems. However, introducing these systems also presented new types of medication errors.[18,19] Although the number of medication errors and potential ADEs has decreased since implementing CPOEs, including basic CDS systems,[20] the effect on actual ADEs has been variable.[21] Therefore, CDS systems should be implemented[10,13,17], and existing CDS systems should be considerably improved[22,23] to solve this ongoing problem.

CDS systems can help alert healthcare professionals to potential ADEs. However, implementing such systems has led to alert fatigue, which causes critical alerts to be overridden along with insignificant events, impairing patient safety.[24] CPOE override rates for hospitalized patients are high, ranging from 49–96% of cases.[24-26] Pharmacist override rates are similar and equally alarming.[27-30] It is important to note that the studied override rates are for traditional or basic medication-related CDS systems, which include checks for drug–drug interactions (DDIs), duplicate therapy, drug doses, and drug allergies.[31] DDI alerts are among the most frequently overridden[26,32], with limited options to turn off some frequently generated alerts.[33,34] Several medication-related CDS systems that consider individual patient characteristics, sometimes called advanced CDS systems, still perform poorly with positive predictive values (PPVs) below 20%.[27] With overrides this high in basic and advanced CDS systems, it is easy to overlook the critical alert that could have prevented an ADE. Fewer alerts are required to prevent ADEs using current knowledge presented in the alerts.

The most significant reason for the high override rates is a lack of contextualization in CDS systems, both in prioritizing[35,36] an alert and the information provided by the alert.[37,38] In computer science, context refers to the idea that a system is capable of sensing and reacting based on its environment. The definition of context provided by Dey is widely cited: "Context is any information that can be used to characterize the situation of an entity. An entity is a person, place, or object considered relevant to the interaction between a user and an application, including the user and applications themselves." Based on this definition, a CDS system providing context attempts to make assumptions about the current situation's relevance, depending on the user's task.[39] Ignoring the patient context can lead

to unimportant, frustrating alerts, causing alert fatigue. However, overlooking the context of the healthcare professional's task leads to alert-workflow mismatches,[24,40] also causing alert fatigue. Although the work of clinical pharmacists is less subject to alert-workflow mismatches than that of intensive care physicians or surgeons, alert-workflow mismatches are a major cause of frustration and alert fatigue.[28]

If a healthcare professional is expected to act on an alert, the CDS system must be aware of the context to provide the right alert to the right healthcare professional at the right moment. Structured development and validation are essential to ensure adequate context is incorporated into the rules used in CDS systems. Two key components of good development strategies are (1) using a multidisciplinary expert panel[41] and (2) offline test and revision cycles.[42] Validation should focus on showing alerts only when necessary and, when shown, providing detailed advice.[42-45]

Although many potential ADEs trigger alerts, many more situations do not trigger CDS alerts.[15] A (potential) ADE is initially detected using a trigger. The start of each clinical rule has a trigger, which is one of the key functional dimensions of CDS systems. The most often used trigger in medication-related CDS systems is "medication order entered."[46] While critical and at the core of basic medication-related CDS systems, it is also restrictive, failing to consider all steps in the medication use process. For example, while ordering inappropriate medication to administer enterally can generate an alert in some CDS systems, registering an enteral feeding tube or nil per os (NPO) instruction does not trigger the system to check if prescribed oral medication is suitable to be given enterally or must be switched to intravenous administration. The same is true for actual ADEs; e.g., a patient with arrhythmia due to drug-induced hypokalemia does not trigger an alert to begin potassium supplementation, ameliorating the ADE.[47] Using triggers other than "medication order entered" is necessary to close the gap between preventable ADEs and appropriate alerts to preclude them.[22]

If triggers other than medication orders are necessary to close the gap, it is essential that the CDS systems have access to additional information. If information is not available in a structured form it should be converted or translated into structured data. Furthermore, if structured data is available, it must be possible to exchange this data between systems and institutions in a structured way.[48] One of the most notorious illustrations of inadequately structured information capture and exchange is the appearance of preventable repeat ADEs. A preventable repeat ADE is unintentional re-exposure to a drug known to harm a patient (e.g., a patient is administered a drug although known to be allergic to it).[49] Although such incidents can seem exceptional and concerning, they are common; the prevalence of repeat ADEs is as high as 30%.[48,50,51] If the first ADE is not registered correctly in the EHR or CPOE, the CDS system cannot generate an alert during represcription or administration. Since 100% correct ADE registration and exchange is an illusion, it is crucial to develop systems to recognize previous ADEs in EHR records and free text and generate alerts to prevent them.

THESIS OBJECTIVE

The objective of this thesis is to investigate whether incorporating context into clinical decision support systems can help improve the detection and prevention of adverse drug events.

THESIS OUTLINE

This thesis begins with a literature review of different CDS systems and their uses (**Chapter 1.2**). **Chapter 2.1** investigates whether adding context to basic CDS systems can improve alerting quality for the most frequently overwritten medication alerts: drug–drug interactions. **Chapter 2.2** investigates whether the context of free text (unstructured data) can help detect ADEs and prevent repeat ADEs. **Chapter 3.1** focuses on adding context to medication-related CDS based on whether a patient has an enteral feeding tube, helping to choose the appropriate medication or medication management and potentially preventing feeding tube-related medication errors. **Chapter 3.2** examines whether medication orders can serve as context to alert physicians to one of the most frequent and mortal electrolyte disturbances in hospitalized patients: hypokalemia.

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CHAPTER 1.2

Clinical decision support systems

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CLINICAL DECISION SUPPORT SYSTEMS

WHAT IS A CLINICAL DECISION SUPPORT SYSTEM?

Clinical decision support includes a variety of tools and interventions computerized as well as non- computerized. Non-computerized tools include clinical guidelines or digital clinical decision support resources like ClinicalKey® or UpToDate®.[1,2] Such clinical decision support (CDS) systems are characterized as tools for information management. Another category of CDS systems sometimes also called basic or simple CDS systems are tools to help focus attention. Examples of such CDS systems include laboratory information systems (LISs) highlighting critical care values or pharmacy information systems (PISs) presenting an alert ordering a new drug and proposing a possible drug-drug interaction.[3,4] Most focus in the past few decades however has gone to tools to provide patient-specific recommendations frequently called advanced CDS or contextualized CDS. Advanced CDS may include, for example, checking drug disease interactions, individualized dosing support during renal impairment, or recommendations on laboratory testing during drug use.

WHY CLINICAL DECISION SUPPORT SYSTEMS?

The quantity and quality of clinical data are rapidly expanding, including electronic health records (EHRs), disease registries, patient surveys and information exchanges. Big data and digitalization however, does not automatically mean better patient care. Several studies have shown that only implementing an EHR and computerized physician order entry (CPOE) has rapidly decreased certain errors, introducing however many more.[5-7] Therefore, high-quality clinical decision support is essential if healthcare organizations are to achieve the full benefits of electronic health records and CPOE. In the current healthcare setting when facing a decision, healthcare providers often do not know that certain patient data are available in the EHR, do not always know how to access the data, do not have the time to search for the data or are not fully informed on the most current medical insights. It is said the healthcare providers often drown in the midst of plenty.[8-10]

Moreover, decisions by healthcare professionals are often made during direct patient contact, ward rounds or multidisciplinary meetings. This means that many decisions are made in a matter of seconds or minutes. Making the decision dependent on the healthcare provider having all patient parameters and medical knowledge readily available at that time of the decision. Consequently, current decisions are still strongly determined by experience and knowledge of the professional. Also, subtle changes in a patients' condition taking place before hospital- or ward admission are often overlooked because clinicians regularly perceive a patient in his current state without taking into account changes within normal range. A computer however, takes into account all data available making it also possible to notice changes outside the scope of the professional and notices changes specific for a certain patient, within normal limits.

TYPES OF CLINICAL DECISION SUPPORT SYSTEMS

To understand literature on the topic of CDS systems and familiarize oneself on the subject it is important to categorize the vast array of CDS systems. Categorization of CDS systems is often based on the following characteristics: system function, model for giving advice, style of communication, underlying decision making process and human computer interaction which are briefly explained below.[11]

The characteristic 'System function' distinguishes two types of functions. Systems determining: *what is true?*: These include purely diagnostic CDS systems like many popular differential diagnosis websites like Diagnosaurus® or WebMD®.[12,13] These CDS systems base their advice on a fixed set of data that is user inputted or readily available. The other type of CDS systems determine: *what to do?*, advising which test to order purposing further differential diagnosis or which drug to prescribe for the patients' current condition. However, this distinction is of limited value as most current integrated CDS systems almost always do both: first determine what is true about a patient and then suggest what to do.

Another characteristic of CDS systems are the way the give advice, being passive or active. Passive CDS systems require the user to do something to receive advice, for example clicking a button or opening a tab. These passive types however, have been abandoned for most part because of their lack of efficacy and dependence of human involvement.[14,15] A challenge of active systems is to avoid the generation of excessive amount of alerts, causing alert fatigue with the user. This topic is discussed further on in the paragraph on alert fatigue. A closely related characteristic commonly used to categorize CDS systems is the style of communication, distinguishing a consulting and critiquing model. In a consulting model the system is an advisor, asking questions and proposes subsequent actions. For example, when entering a medication order, the computer asks for the diagnosis and advises the right dose or an alternative treatment. A critiquing system lets the user decide the right dose for itself and only afterwards alerts the user that the dose prescribed for this therapy is too low.

Human computer interaction is another clinical decision support system characteristic. How does a user interact with the computer? Historically CDS systems were slow, difficult to access and difficult to use. However, modern day computing power, electronic health record integration and computer mobility have made these problems of the past. However, human computer interaction is still a good way to categorize CDS systems describing EHR integration or overlay, keyboard or voice recognition and advice by means of pop-ups, acoustic alarms or messaging systems.

The last commonly used characterization of CDS systems, and perhaps the most interesting, is the underlying decision-making process or model. The simplest models are problem-specific flowcharts encoded for computerized use, these are discussed further on. With the availability of additional statistical models, mathematical techniques and increasing computing power, much more complex models have been researched and used

since, like Bayesian models[16,17], artificial neural networks[18], support vector machines[19] and artificial intelligence[20]. Many of these systems are used to improve prediction of outcome, prioritize treatment or help choosing the best course of action. Use of such systems in practice however is delayed mainly because of trust issues towards 'black box' systems. If a computer tells you to start drug A for a patient based solely on a mathematical model, without a guideline to back it up, are you convinced to do it? Linked to the major trust issue towards 'black box' systems is the current model of evidence based medicine and concurrent guidelines based on these studies. Are you willing to ignore an international guideline saying you should start a patient on drug A only because your CDS system says you should start the patient on drug B?

Decision tree models are the oldest but still most used models in clinical practice today. CDS systems using such models use a tree-like model of decisions consisting of multiple steps of 'if then else' logic. Figure 2 shows an example of such a decision tree model. These models have the advantage of being interpretable by humans and follow logical steps based on conventional clinical practice guidelines. Such decision tree models are also called clinical rules (CRs), computer-interpretable guidelines (CIGs) or decision support algorithms.[15] Instead of predicting outcome or best therapy, a CDS system only automatizes information gathering and provides advice in accordance with a guideline.

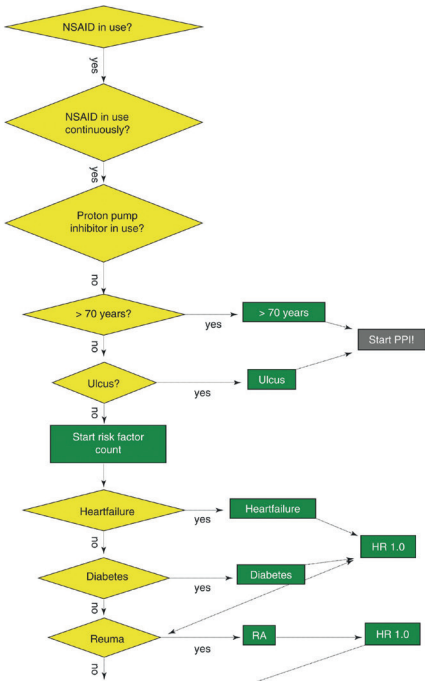

FIGURE 2. *Part of the clinical rule gastric protection, represented in GLIF, created in CDS system Gaston Pharma®. Picture adopted from Scheepers et al. 2009[14]*

MEDICATION RELATED CLINICAL DECISION SUPPORT SYSTEMS

From a historical point of view, medication related CDS system seem to go the farthest back and are likely to have the largest potential for benefit.[21] They date back as long as the 1960s.[22] They supported pharmacists with drug allergy checking, dose guidance, drug-drug interaction checking and duplicate therapy checking. Medication related CDS system took further shape when directly linked to computerized physician order entry (CPOE).[23] CPOE being the system that enabled physicians to prescribe medication using electronic entry. The combination of CPOE and CDS system helped physicians choose the right drug in the right dose and alert the physician during prescribing if for example the patient is allergic. Combining CPOE with basic medication related CDS system meant a giant leap in safer medication prescribing.[24,25] However, all of the checks mentioned above follow simple 'if then else' logic and do not combine multiple patient characteristics when producing alerts. This addition came with the introduction of contextualized medication related CDS systems. In older literature there are also references to the use of advanced CDS systems, referring to contextualized CDS systems using one specific contextual modulator being for example renal insufficiency.

Complexity of contextualized medication related CDS systems can vary widely from only including one contextual modulator such as renal function to including dozens of modulators such as multiple medication dependent modulators(dose, co-medication, chronology, lag-time etc.), multiple patient characteristics and multiple dynamic patient parameters (vital signs, lab results etc.). Such contextualized CDS systems follow and combine multiple decision tree based models and can assist the physician in dosing medication for patients with renal insufficiency and drug disease interactions for example, provide guidance for medication-related laboratory testing and perform drug-disease contraindication checking.[23,26] Contextual modulators incorporated into medication related CDS systems rose steadily in the past few decades including pharmacogenetics and more and more drug disease interactions.

Many current EHRs with integrated CDS system however, still fail to provide guidance relevant to the specific patient receiving care, poorly presenting data and causing alert fatigue to health care providers.[27] One of the main issues with these systems is that they combine only one or two contextual modulators to provide alerts, thereby only increasing the number of alerts. For example, prescribing nortriptyline to a patient with hepatorenal syndrome and being an intermediate metabolizer of CYP2D6 will generate a total of three alerts with three different advices. An advice on how to dose nortriptyline in a patient with renal insufficiency, another alert with an advice how to dose nortriptyline in patients with liver failure and last but not least an advice how to start treatment in a patient being an CYP2D6 intermediate metabolizer. So which advice should we follow? Therefore, effort should be made into combining multiple contextual modulators and clinical rules to provide one correct advice to the healthcare provider. Designs should incorporate the

engagement of all clinicians involved in the delivery of health care and combine multiple patient characteristics and context simultaneously, to ensure that CDS system are actually helpful to clinicians, rather than interrupt health care delivery.

CHALLENGES IMPLEMENTING CDS SYSTEMS

CDS systems are an evolving technology with potential for wide applicability, to individualize and improve patient outcome and health care resource utilization.[24,28] However, to make CDS system more helpful it requires thoughtful design, implementation and critical evaluation.[29]

As mentioned earlier the promise of CDS systems has been around since the 1960s. In 2008, Simon *et al.* still found that the vast majority of EHRs across the U.S.A. implemented little or any decision support.[30] A recent survey send out to all Dutch hospital pharmacies showed similar disappointing results, only 48% of them using some kind of contextualized CDS system.[31]

Such alarming results were one of the main reasons the American Medical Informatics Association (AMIA) published the Roadmap for National Action on Clinical Decision Support. The paper acknowledged six strategic objectives, divided into three main pillars, for achieving widespread adoption of effective clinical decision support system capabilities.[32] The three main pillars being: 1. High Adoption and Effective Use. 2. Best Knowledge Available When Needed. 3. Continuous Improvement of Knowledge and CDS system Methods.[32] In the following paragraphs these three pillars will be highlighted to give an overview of tasks and challenges that lay ahead.

HIGH ADOPTION AND EFFECTIVE USE

To ensure high adoption and effective use, it is important to fine-tune the CDS system in order to suit end-users wishes. Only then alert fatigue can be minimized.

Alert fatigue

Alert fatigue is the concept of poor signal to noise ratio caused by CDS system with an active alerting mechanism. Alert fatigue is defined as the "Mental fatigue experienced by health care providers who encounter numerous alerts and reminders from the use of CDS system."[33] Alert fatigue causes physicians to override 49-96% of the current medication safety alerts from basic CDS system as well as advanced medication related CDS system. The main reasons for overriding alerts are: low specificity, unnecessary workflow disruption and unclear information.[34,35] Many of these aspects are caused by lack of user- and patient context. More on the subject of context can be read in the paragraph on context factors, later on.

Because CDS systems are offering more and more options characterization of the CDS system itself is not enough. Characterization of the clinical rules used by decision tree CDS systems is also key to understand the background of alert fatigue. In the upcoming paragraphs the taxonomy of clinical rules is explained using two fundamental concepts, being triggers and contextual factors.

Triggers

In an effort to characterize clinical rules, Wright *et al.* used four functional categories: triggers, input data, interventions and offered choices. Triggers were identified as one of the key functional dimensions of CDS system and are the start of each clinical rule. Wright and colleagues reviewed and analyzed their own extensive rule repository, using these four functional dimensions to identify and quantify the use of different taxonomic groups. They identified nine different triggers. However, by far the trigger most often used is the 'order entered' trigger, accounting for 94% of all the studied clinical rules and 38% of all clinical rule types. Combined with the knowledge that a patients' drug list is also the most used 'input data element' in all of the studied rules, medication orders (MOs) and drug lists seem to play a key role in CDS system currently used.[36,37]

Contextual modulators

'Context', in computer science, refers to the idea that a system, in our case a clinical decision support system, is both capable of sensing and reacting, based on its environment. An often provided definition of the term 'context' is the one set by Dey, being: "Context is any information that can be used to characterize the situation of an entity. An entity is a person, place, or object that is considered relevant to the interaction between a user and an application, including the user and applications themselves". Using this definition a system providing 'context' also tries to make assumptions about the current situation in relevance, dependent on the user's task or patient's-status.[38]

Riedmann *et al.* performed a review of literature and subsequently performed an international Delphi study to identify the most important context modulators to medication related CDS system.[39,40] The most important context factors found were 'severity of the effect', 'clinical status of the patient', 'complexity of the case' and 'risk factors of the patient'. All of these context factors are gained from input data elements such as diagnosis, prior disease history, laboratory results and hospital unit.[36]

Another study group of Berlin *et al.* found that the most targeted clinical tasks of clinicians were associated with drug dosing (46%) and drug treatment (22%).[41,42] These findings are in agreement with the study of Wright *et al.* although using a completely different taxonomy.[41]

When combining the results from the studies performed by Wright *et al.* and Berlin *et al.*, the most CDS system targeted clinical tasks were 'start of treatment' and 'dose

adjustment'. As stated earlier, medication ordering was the most frequently used trigger to a clinical rule and a patient's drug list was the utmost used and most easily available input element. Therefore, providing the right context to medication orders using the drug list should be an important priority. Context factors like 'severity of the effect', 'clinical status of the patient', 'complexity of the case' and 'risk factors of the patient' found by Riedmann *et al.* are logical context factors from a physician's point of view. However, adding such context only adds value when trigger related contexts like 'start of treatment' and 'dose adjustment' are also included. Moreover, data input like those described by Riedmann *et al.* is not always distinct and readily available in the EHR.[36,39,41]

In our own experience, gained in the Netherlands, integrated medication related CDS system are still unable to correctly interpret the simple contextual modulators of medication orders. During development and validation of clinical rules, basic contexts like start of new treatment or dose adjustment proved to be elusive and are a frequent cause of suboptimal positive predictive value (PPV) and sometimes suboptimal negative predictive value (NPV). Experts also frequently disagree upon the definitions and clinical relevance of these contextual modulators.[43,44] Is a medication order a dose adjustment or start of new treatment? An example is a digoxin order. If the clinical task would be starting a patient on digoxin therapy, the CDS system should advice the prescriber on ordering serum potassium levels, perform therapeutic drug monitoring and review new drug-drug interactions. However, entering the same digoxin order to change drug administration time or change drug form, the above monitoring is not applicable. Providing the physician or pharmacist with notifications during this process would cause frustration and alert fatigue.[45]

BEST KNOWLEDGE AVAILABLE WHEN NEEDED

The second pillar in the Roadmap provided by the AMIA is best knowledge available when needed. The pillar contains three key challenges:

- When needed: Integration in clinical workflow
- Knowledge is available: so it has to be written, stored and transmitted in a format that makes it easy to build and deploy CDS system interventions
- Best knowledge: Only CDS system which provides current and additional information has potential

When needed: Integration in clinical workflow

A key success factor of CDS system is that they are integrated into the clinical workflow. CDS system not integrated into clinical workflow will have no beneficial effect and will not be used.[46] Messages should be presented at the moment of decision-making, though with as less disturbance for the physician as possible. Therefore, different alert mechanisms (pop-up, automatic lab order, prescription order, emails, etc.) should be developed, suitable for different alerting priorities.[47] Understanding how to prompt physicians successfully at the

point of care is a complex problem, and requires consideration of technological, clinical, and socio-technical issues. As mentioned earlier, interruptive (active) alerts show significantly higher effectiveness than non-interruptive (passive) reminders.[48] Additionally, a greater positive impact was observed when recommendations prompted an action and could not be ignored.[49] Thoroughly understanding the clinical workflow and users' wishes strongly increases the probability for success.[49] One of the more recent attempts to incorporate CDS system into clinical workflow was to incorporate CDS system advice into checklists often used in ward rounds.[50] An example of such a particular system is Tracebook. This is a process-oriented and context-aware dynamic checklist, showing great promise and good user acceptability.[51]

Knowledge is available

One of the other major challenges of effective CDS system adaptation is keeping the clinical rules up to date.[49] However, keeping these clinical rules up to date is a massive time and money-consuming task. Therefore, sharing clinical rules seems to be a sensible and financially attractive choice. One of the strategic objectives described in the roadmap was to create a way to easily distribute, share and incorporate clinical knowledge and CDS system interventions into own information systems and processes. With this concept clinical rules could be externally maintained, making a huge leap in efficacy of development and maintenance. A healthcare provider could then just subscribe to certain clinical rules. This should work in "*such a way that healthcare organizations and practices can implement new state of the art clinical decision support interventions with little or no extra effort on their part*".[32]

Today many clinical rule repositories exist, however none of them are fully functioning. They rely on software vendors to rebuild them into their own CDS system modules. Progress on this objective has been especially problematic when attempting to make or share clinical rules outside an ecosystem of the software vendor.[52] The progress being made using integrated EHR systems, also called second phase CDS system, is commendable however; it strictly limits sharing clinical rules outside of the EHR ecosystem. Newer standards-based systems, third phase and service model systems like the Arden syntax, GLIF, SAGE and SEBASTIAN solve many issues concerning sharing clinical rules.[53,54] Although all very good initiatives, none of the architectures have really found use in clinical practice.

One of the issues in sharing fully functioning clinical rules are the difference in clinical terms as well as language. Clinicians starting to program clinical rules should keep in mind using standardized terms to make exchange of their CDS system modules possible. Using standardized clinical health terminologies like SNOMED CT would resolve a lot of issues surrounding sharing CDS system content.[55]

One of the other challenges however is to standardize definitions of context, as these are essential to minimize signal to noise ratio. To study the obstacles left to make sharing a

reality, an initiative was started to develop clinical rules which would work across different EHRs, CPOEs, PISs and institutions using the GASTON framework.[56] The framework, derived from GLIF architecture, facilitates sharing guidelines and facilitates integration with institution specific medical knowledge sources and information systems such as EHRs and CPOEs without changing the clinical rules themselves. The most important lesson learned from this project was that despite consensus on the content of a clinical rule, local adaptation was always necessary to achieve sufficient specificity of the alerts.

BEST KNOWLEDGE & CONTINUOUS IMPROVEMENT OF KNOWLEDGE AND CDS SYSTEM METHODS

To ensure the best knowledge and retain continuous improvement, validation and verification is indispensable. Much research has been done on the validation of clinical rules itself and focuses on clinical relevance of the recommendations produced by the CDS system. However, to assure correct clinical rules and recommendations we depend on data from the EHR and the correct functioning of the CDS system. The next few paragraphs will give an overview over the levels of validation and verification of CDS systems.

CDS SYSTEMS VERIFICATION AND VALIDATION

Successful adaptation and functioning of clinical rules vastly depends on the CDS system used. Tendering, choosing or implementing a new CDS system requires a comprehensive user requirement specification (URS) or user requirement documentation (URD). A URS specifies what the users of the software expect the software to do. It is often seen as the contract between the user and the software supplier. Not explicitly or correctly stating user requirements for a software system is the major factor contributing to failed software implementations and massive budget overruns. Maybe not a very appealing job for clinicians, we cannot stress enough the importance of working together with IT personnel to write an all-encompassing URS. Adding or improving functionality afterwards is difficult and costly.

It is important to test all functions of software products such as CDS system. Deepening the topic of software verification and validation requires a book on its own. However, to prevent running into issues during clinical rule development and use of the CDS system in practice it is key to perform software verification and validation using the URS and lower level specifications. Software validation and verification can be performed at many levels using many tools. If your hospital does not have IT personal qualified to plan and perform software verification and validation it is highly recommended to hire external help. Thorough verification and validation of the CDS system software can save expenses and spare frustration later on or even failure of implementation.

When using a CDS system we should keep in mind that a CDS system relies on high quality data to work. Assuring the correct collection of data and their quality is vital before starting to program the clinical rules themselves. A part of the requirements should therefore be a thorough description and testing of items to be used in the clinical rules. If you state: "the system must present the age of a patient" for example; the CDS system probably will present the age of the patient in years. Designing clinical rules using this parameter however for a neonatal care unit could be unwanted and unspecific. Testing if items used in clinical rules result in the expected answer requires clinical knowledge, often scares IT personnel. Clinicians eager to program clinical rules themselves are therefore encouraged to assist in this stage of CDS system validation.

After the successful implementation of the CDS system itself we are ready to start building our own clinical rules.

DEVELOPMENT AND VALIDATION STRATEGY

Key to preventing alert fatigue in active CDS system is structured development and validation of clinical rules. Much has been published on the validation of these clinical rules focusing on providing maximal clinical relevance of the recommendations outputted by the CDS system.[47,57-59]

Two key components of a good validation strategy described in most studies are: (1) the use of a multidisciplinary expert panel as well as (2) offline test and revision cycles.[58] A framework was published by McCoy *et al.*, describing a potentially effective method for assessing clinical appropriateness of medication alerts. A key attribute of this framework is that it determines appropriateness at the time of a triggered alert and by applying expert knowledge.[60] Weingart *et al.* examined a subset of all displayed alerts to determine alert validity and expert agreement with overrides, although no measures of unintended adverse consequences were reported.[58] Sucher mentions factors that need to be tested, such as verification, validation and worst case testing, but these factors are not explained in detail.[59] A practical validation approach is described by Osherhoff *et al.*, using cases and testing scenarios to validate clinical rules.[47] This method however has limited usefulness due to lack of a detailed description of the method and outcome. To prevent alert fatigue, CDS system implementers must monitor and identify situations that frequently trigger inappropriate alerts and take well-defined steps to improve alert appropriateness.[60] Studies examining CDS system content validation often lack a complete and reproducible method that is demonstrably leading to appropriate alerts.

Strategy for development and validation of clinical rules

Below we describe a four-step strategy to develop and implement clinical rules, which we ourselves use as part of development.[57,61]

Step 1: Technical validation

The objective of this step is to determine whether a clinical rule functions as we expect it to do. Are the parameters in the CDS system linked correctly to the EHR and are we using technically valid definitions. Of course the first step starts by designing a clinical rule. Most often such a clinical rule is based on an evidence-based medicine (EBM) guideline. The EBM guideline is first translated into a computer-interpretable format with measurable and specific parameters. This regularly requires translating clinical terms used in guidelines to standardized clinical terms before use. For example, how to define diarrhea? Is it enough a patient has watery stool or should it also be more than three times a day? Such definitions are not solved using only standardized terms. After definitions are clear and build into the clinical rule the clinical rule is tested on a historical EMR database. Subsequently, results are analyzed to determine the amount of true positives (TPs) and true negatives (TNs). These results are discussed in a plenary meeting together with an expert team. Here possible improvements are identified, which could later on be implemented. When the objectives are met (positive predictive value (PPV) > 90% and negative predictive value (NPV) >95%), the second step of the development strategy is started.

Step 2: Therapeutic retrospective validation

The second step is intended to check whether the alerts produced by the CDS system are clinically relevant, useful and actionable. This step of therapeutic validation is of greatest importance for user acceptance further on. Although alerts at this stage are technically valid and based on evidence-based guidelines, health care professionals may not always consider them useful or relevant. This step starts with a meeting between the building team and the expert team to discuss the therapeutic value of the alerts. The expert team should include experts on the subject at hand from different medical disciplines. Moreover, opinion leaders from the clinic should also be included. The expert team reviews all of the alerts generated and classifies them as being relevant or not. Differences between theory and practice are discussed and the expert team formulates modifications to the clinical rule. After modifications are implemented, the clinical rule is tested in the same manner as in step 1 using the same set of patients from historical EHR database. After this test, outcome is once again evaluated by the technical team and expert team together in order to maximize therapeutic PPV and NPV.

Step 3: Pre-implementation prospective validation

The third step is used to prepare the CDS system and clinical rule for implementation in practice. The CDS system is linked to a real live EHR, allowing to generate alerts of actually admitted patients. Adaptations are made to assure timely alerting and integration into clinical workflow. The expert team is consulted once again however now focusing on the content of the message (e.g., proposal, command), the recipient of the message (e.g., nurse,

physician, pharmacist), the frequency (e.g., once daily, continuously) and the alerting method (e.g., on-demand, automatic). When the rule is refined on these issues, it once again returns to step 1 to proceed through the validation cycle. After completing step one and two again, the rule is implemented into operation and made accessible to a selected group of users to do the final validation. Based on user feedback some final minor technical adjustments are mostly directed to optimize user satisfaction. Frequently, the issues requiring adjustment are the result of only testing the clinical rule in a retrospective setting on a static database instead of prospective on a dynamic real live EHR database. Depending on the frequency of alerting, usually after two months, the results from the prospective testing are evaluated by the technical and expert team together to calculate the final positive predictive value. Now the clinical rule is ready for implementation in daily practice.

Step 4: Post-implementation prospective validation

The fourth step, after implementation of the clinical rule in daily practice, is continuous maintenance. This step corresponds to the third pillar of effective CDS system implementation suggested by Osherhof and colleagues in their Roadmap.[32] In this step the clinical rule is monitored while operational. Monitoring consists on reviewing performance, follow-up and PPV. The step also encompasses technical and therapeutic maintenance to ensure continuous accuracy of the alerts. We found that every clinical rule needs adjustments after implementation in practice, which were not foreseen during the development phase (step 1-3). First, technical adjustments may be necessary due to updates or new functionalities in the CDS system or EHR. These technical adjustments are developed, validated and implemented by the technical team. When the changes also had therapeutic consequences, the expert team was consulted. Secondly, the content of the clinical rule should be updated regularly, due to changes in the underlying evidence-based medicine or end-users preferences. For example when a new version of the clinical guideline was available, clinical rules were checked and differences reviewed. This step finalizes the strategy, through continuously optimizing suitability of the rule in practice.

Adaptation in practice

The adaptation of a CDS system in practice is a key component to success. The validation strategy described above especially benefits from including experts in all of its development cycles. These experts and opinion leaders help support the adaptation of clinical rules in practice and are the main success factor of this strategy.

FUTURE PERSPECTIVES

This chapter shows that clinical decision support systems can definitely support the use of clinical data science in daily clinical practice. However, adoption in practice remains a slow process and many are still reinventing the wheel instead of supporting national initiatives. Decision support systems today mainly use the 'if then else' logic. And even using this method, validation is already very time-consuming and complex.

We are very curious to see combinations of systems using tree-based logic using current EBM guidelines and suggestions made using machine learning models or even deep learning models. It is a great and promising challenge to make healthcare really benefit more from big data, draw conclusions humans haven't drawn themselves. However, validation, acceptance and adaptation of 'black box' systems will require a paradigm shift, challenging the basic principles of current day EBM practice. Nevertheless, believe in decision support keeps attracting health care professionals to work with these powerful and promising systems.

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2

DETECTION OF POTENTIAL ADVERSE DRUG EVENTS

CHAPTER 2.1

Contextualized drug-drug interaction management improves clinical utility compared to basic drug-drug interaction management in hospitalized patients

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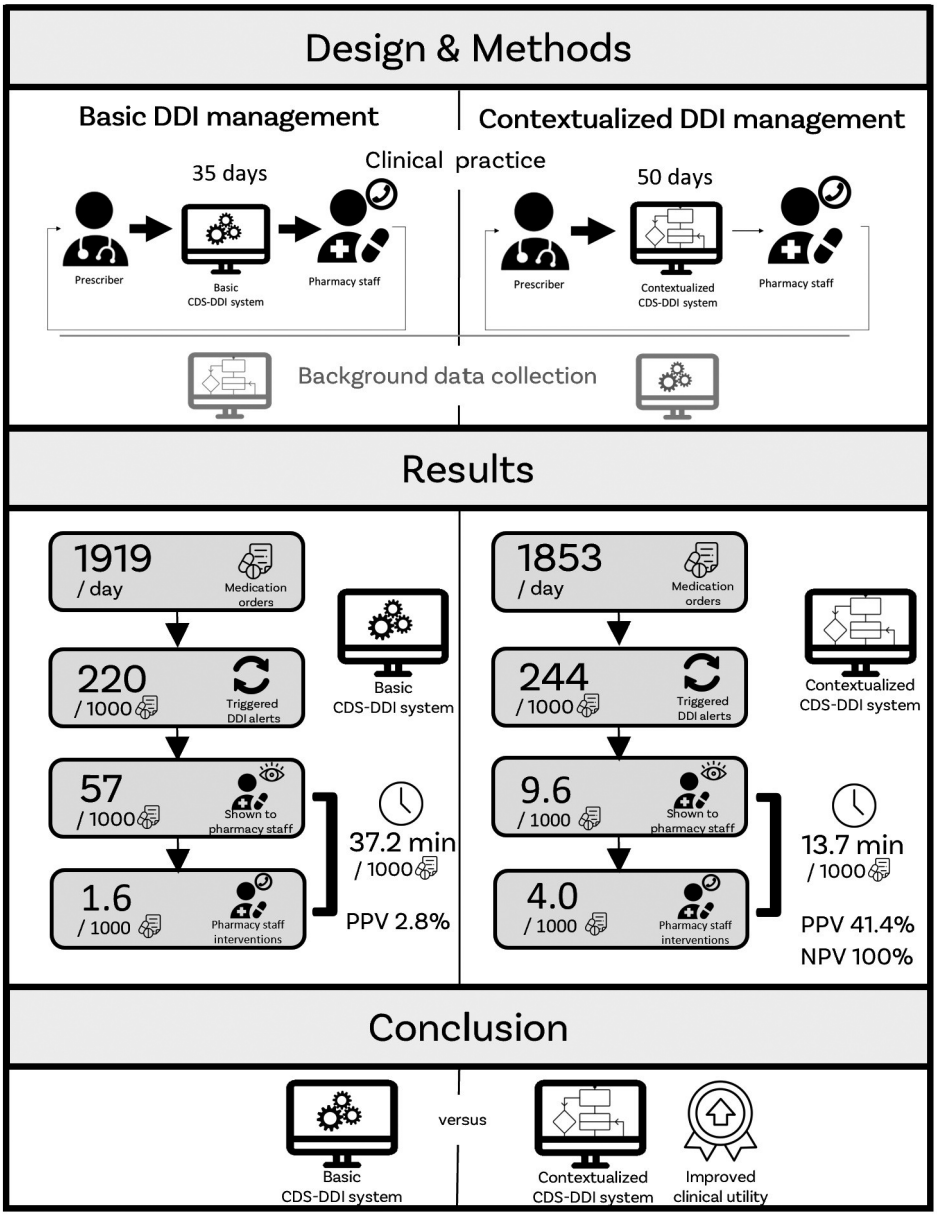
GRAPHICAL ABSTRACT



ABSTRACT

INTRODUCTION AND OBJECTIVE

Drug-drug interactions (DDIs) frequently trigger adverse drug events or reduced efficacy. Most DDI alerts, however, are overridden because of irrelevance for the specific patient. Basic DDI clinical decision support (CDS) systems offer limited possibilities for decreasing the number of irrelevant DDI alerts without missing relevant ones. Computerized decision tree rules were designed to context dependently suppress irrelevant DDI alerts.

METHODS

A crossover study was performed to compare the clinical utility of contextualized and basic DDI management in hospitalized patients. First, a basic DDI-CDS system was used in clinical practice while contextualized DDI alerts were collected in the background. Next, this process was reversed. All medication orders (MOs) from hospitalized patients with at least one DDI alert were included. The following outcome measures were used to assess clinical utility: positive predictive value (PPV), negative predictive value (NPV), number of pharmacy interventions (PIs)/1,000 MOs and the median time spent on DDI management/1,000 MOs.

RESULTS

During the basic DDI management phase 1,919 MO/day were included, triggering 220 DDI alerts/1,000 MOs; showing 57 basic DDI alert/1,000 MOs to pharmacy staff; PPV was 2.8% with 1.6 PIs/1,000 MOs costing 37.2 min/1,000 MOs. No DDIs were missed by the contextualized CDS system (NPV 100%). During the contextualized DDI management phase 1,853 MO/day were included, triggering 244 basic DDI alerts/1,000 MOs, showing 9.6 contextualized DDIs/1,000 MOs to pharmacy staff; PPV was 41.4% ($p<0.01$) with 4.0 PIs/1,000 MOs ($p<0.01$) and 13.7 min/1,000 MOs.

CONCLUSION

The clinical utility of contextualized DDI management exceeds that of basic DDI management.

INTRODUCTION

Drug-drug interactions (DDIs) frequently occur in hospitalized patients: 65-90% of these patients are exposed to one or more potential DDIs.[1-3] Mismanagement of DDIs can lead to adverse drug events or reduce the efficacy of drugs involved.[4] Healthcare providers cannot be expected to memorize the thousands of known DDIs and the management thereof[5-7] Clinical decision support (CDS) systems have been added to computerized physician order entry (CPOE) and pharmacy information systems to assist healthcare professionals in alerting and managing the risks of potentially harmful medication combinations. Such DDI-CDS systems, also called basic medication-related CDS systems[8], trigger alerts for the pair-wise combination of the drugs involved. In practice, however, such DDI alerts are frequently overridden as most alerts are considered to be irrelevant for that specific patient.[9-13]

Too many irrelevant alerts can lead to alert fatigue[9,13-15], described as a 'mental state being the result of too many irrelevant alerts consuming time and mental energy, which can cause important alerts to be ignored along with clinically unimportant ones'[16]. Basic DDI-CDS systems have limited options for suppressing irrelevant DDI alerts; other than turning DDI alerts off for specific drug combinations. This approach has limited opportunities for improving specificity without compromising sensitivity.[17-24] Recent studies concluded that CDS systems should have greater flexibility to customize DDI alerting especially by adding contextual modulation, also called specificity modulation.[25-27] The term contextual modulation comes from neurobiology; being the change in the neurons responsiveness to a stimulus caused by context.[28] In the setting of medication related CDS alerting, contextual modulation changes whether or not a triggered alert is displayed and how, based on context.

Contextualized CDS systems, also known as advanced CDS systems, offer more possibilities for suppression of irrelevant alerts since these systems incorporate context. The most important forms of context are workflow context and clinical context which, can by using information available in the electronic health records (EHRs) prioritize alerts and/or suppress them.[29-32] Improving the specificity of DDI alerts has been studied using different types of clinical contexts: admission wards or treating medical specialties[33,34] (e.g. not showing QT prolongation DDI alerts for intensive care patients); patient parameters such as age, blood pressure and or laboratory results[12,33,35-37] (e.g. not showing DDI alerts for potassium + potassium/sparing diuretics in patients with hypokalemia); only showing alerts above a specific dose (e.g. fluconazole > 100 mg + immunosuppressant) 38; and co-administered drugs[38,39]. Clinical decision support systems using the workflow context can be programmed to better fit workflow and usability[32,33,40,41], improve DDI alert triggering[42] and stop or reduce the repetition of already presented alerts[33,43]. Overall, these studies showed reductions of 50-92% of the DDI alert burden.[33,35]

Most studies have focused on reducing the number of irrelevant DDI alerts in either using clinical or workflow contexts.[22,23,39] Only two studies investigate the effects of

combining these two.[33,35] Moreover, only two studies have explored the impact of such optimizations on the sensitivity or negative predictive value.[17,18] Therefore, a set of computerized decision tree rules (algorithms) was designed to combine clinical and workflow contexts to suppress irrelevant DDI alerts. These rules were programmed on top a of regular DDI knowledge base. The contextualized DDI-CDS management system utilizes different patient parameters, laboratory values, drug doses and previous evaluations to contextualize and assess triggered DDI alerts. This study aimed to compare the clinical utility of contextualized DDI management to that of basic DDI management in hospitalized patients.

METHODS

STUDY DESIGN

A single-center prospective crossover study was performed to compare basic DDI-CDS management to contextualized DDI-CDS management in a clinical pharmacy setting. The first phase was the basic DDI phase, the second phase being the contextualized DDI phase. The basic DDI phase included basic DDI alerts used in clinical practice, while contextualized DDI alerts were gathered in the background, referred to as background data collection. In the contextualized DDI phase, this process was reversed. The basic DDI management phase lasted from the 10th of August 2020 to the 13th of September 2020 (35 days), followed directly by the contextualized DDI management phase from the 14th of September 2020 to the 2nd of November 2020 (50 days); this last phase was longer to perform an adequate number of time measurements of the pharmacy interventions. Prescribers were not informed about the change in the clinical pharmacy DDI management process. The study was declared not subject to Research Involving Human Subjects Act (non-WMO) by the ethics committee of the Catharina Hospital.

STUDY SETTING

The study was performed in the clinical pharmacy at the Catharina Hospital Eindhoven, a 700-bed teaching hospital in the Netherlands. The hospital used HiX® (version 6.1 HF105 and HF108, Chipsoft BV, Amsterdam) as its electronic health record (EHR) system. All relevant medical data are ordered and stored in this system, including CPOE for inpatient and outpatient settings. Smart CPOE ordering, which uses predefined orders and order sets, prevents the occurrence of predominantly time-dependent DDIs. The integrated CDS system offered by the CPOE was used as the basic DDI-CDS system. The basic DDI-CDS system had one type of alert-suppression possibility: turning specific DDI alerts off. Before the start of the study, a set of DDI alerts was already suppressed, having been considered irrelevant by a team of prescribers and hospital pharmacists, included in table S1.

Gaston Pharma® (version 2.8.2.100, Gaston Medical®, Eindhoven) was used to develop and generate the contextualized DDI alerts. Before the start of the study, as a technical validation, two weeks of DDI alerts were matched assuring that without contextualization both systems triggered the same alerts. Followed by three months of technical validation of the developed meta-rules. Gaston Pharma® has been used to provide medication-related CDS in addition to G-standard knowledge base in the Catharina Hospital content since 2006. However, it has not been previously used for DDI management. Costs and return on investment analysis of this system have been published previously.[33] Previously developed clinical rules partially overlapped basic DDI alerts, included as italic type in table S1. The contextualized CDS system can suppress DDI alerts based on the clinical context, including laboratory values, medication order details, outpatient drug-drug combinations and patient demographics. The CDS system could also suppress alerts based on previous evaluations of the DDI, cluster alerts based on advice, medication type or other characteristics.

Hospital pharmacy staff consisted of twelve (senior) hospital pharmacists (HPs), four hospital pharmacists in training and around fourty pharmacy technicians. Daily pharmaceutical services, including DDI management, were performed by four x 0.3 full-term equivalent (FTE) hospital pharmacists and twelve FTE pharmacy technicians on a ward basis. All of the pharmacy staff were already trained to use the contextualized CDS system before the start of the study.

STUDY INCLUSION

The study included all medication orders (MOs) of patients hospitalized with at least one DDI alert triggered by the basic DDI-CDS system during basic as well as contextualized DDI management phase. A MO was defined as a new prescription or any change to an existing prescription (i.e. a dose adjustment).

BASIC DRUG-DRUG INTERACTION MANAGEMENT PROCESS

Table 1 (lefthand side), shows the key system and process details for the basic DDI management process. Figure S1 panel A, B and C give an overview of DDI alert presentation in the basic DDI-CDS system. If the MO for one or both interacting drugs was changed, the DDI alert was shown for each MO during evaluation. Therefore, in most cases, the same DDI alert was shown twice.

TABLE 1. *Similarities and differences between drug-drug interaction clinical decision support management process and system for both phases*

Basic DDI management phase	Contextualized DDI management phase
Same for both phases	
Basic DDI-CDS system in use for physicians	
G-standard knowledge base [a]	
Pharmacy technicians adjusted administration times of drugs without consulting physician or hospital pharmacist	
Different for both phases for clinical pharmacy staff	
Basic DDI-CDS system integrated into EHR system	Contextualized DDI-CDS system on top of EHR system
'Real-time' DDI alert generation	'Batch-wise' DDI alert generation
DDI alerts were shown to prescriber, pharmacy technician and hospital pharmacist in that order	DDI alerts were shown only to pharmacy technician or only to hospital pharmacist depending on applicability
Communication possible between physician and clinical pharmacy staff in the DDI alert note	No communication possible between physician and clinical pharmacy staff
Workflow context suppression	
DDI alerts were shown paired to MOs [c]	DDI alerts were shown independent of MOs [d]
With each type of MO change (prescriber, administration time; route of administration etc.) the DDI alert was shown	DDI alerts were shown once to pharmacy staff and thereafter only if daily dose of one of the interactions drugs was changed [e]
MOs of actionable absorption time-dependent DDIs alerts were changed by pharmacy technician; changes checked by second and thereafter by hospital pharmacist	MOs of actionable absorption time-dependent DDIs alerts were changed by pharmacy technician and then checked by contextualized DDI-CDS system
Clinical context suppression [b]	
DDI alerts could be turned off	DDI alerts could be suppressed depending on specific clinical context (Table 2)
DDI alerts were shown if one of the interacting drugs was already stopped in last 24 hours	DDI alerts were not structurally shown when one of the interacting drugs was already stopped; only if applicable [f]
Clinical rule alerts overlapping part of DDIs were partly shown [g]	Clinical rules alerts overlapping part of DDIs were not shown [g]

[a] G-standard knowledge base which amongst others includes drug-drug interaction (DDI) assessments used nationally in the Netherlands [44]
[b] contextualization included suppressing DDI alert not applicable within the given context and also adding additional information form the electronic health record (EHR) to manage the DDI alert if shown. All general as well as specific clinical contextualization is shown in Table 2 and Table S1.
[c] Evaluation of medication alerts including DDI alerts was shown paired to an medication order (MO). (e.g. DDI alert is shown when evaluating metoprolol MO and DDI alert is shown when evaluating paroxetine MO)
[d] The contextualized system showed DDI alerts not paired to MOs (e.g. DDI alert for metoprolol + paroxetine was shown once) as general suppression was done based on the Anatomical Therapeutic Chemical (ATC) codes of drugs appearing in multiple MOs and DDI alerts were only shown 'again' if daily dose of one of the interactions drugs was changed
[e] DDI alerts only reappeared if medication and daily dose were changed, changing from 'if necessary use' to regular use or from 'one time use' to regular use were defined as dose changes. Multiple MOs for the same drug were always clustered to show one alert; e.g. haloperidol 10 mg + 1 mg + amiodarone 200 mg clustered to show a single alert for haloperidol with amiodarone
[f] DDIs found to be clinical relevant when one of the drugs was stopped (perpetrator) included cytochrome P450 (CYP) inhibitors with long half-life: hydroxychloroquine (100 days), chloroquine (28 days), fluoxetine (15 days) and amiodarone (150 days) and CYP inducers (28 days): rifampicin, primidone, phenytoin, phenobarbital, carbamazepine, efavirenz, hypericum and ritonavir.
[g] Full list of clinical rules used and the overlap with DDI alerts is included at the bottom of Table S1 in italic type
DDI: drug-drug interaction; CDS: Clinical decision support; EHR: electronic health record; MOs: medication orders

Contextualized drug-drug interaction management process

The basic DDI-CDS system offered the option to add text to the alert using the alert comment box. Alerts, including comments, were shown to the prescriber, pharmacy technician and hospital pharmacist, in that order. The alerts themselves were the same for each healthcare professional, text was differentiated. The alert text presented to the prescriber and hospital pharmacist were those included in the G-standard knowledge base. Pharmacy technicians were presented a locally written alert text. The local alert text contained instructions regarding which specific parameters should be checked in the EHR and added to the alert comment box. If instructed in the local text, the pharmacy technician could forward the DDI alert to a hospital pharmacist. Based on all gathered information, the hospital pharmacist could then decide whether to contact the prescriber.

Drug-drug interactions affecting drug absorption are called absorption time-dependent DDIs alerts (e.g. oral ciprofloxacin binding calcium). If administration times needed to be changed to prevent this type of DDI, a pharmacy technician would change administration times without contacting the prescriber. A different pharmacy technician and thereafter the hospital pharmacist evaluated if administration times were changed correctly. The process of DDI evaluation was continuous between 08:00 and 17:30, however medication orders triggering DDI alerts prescribed after 14:00 were evaluated by clinical pharmacy staff the next day.

Table 1 (righthand side), shows the key system and process details for the contextualized DDI management process. In contrast to the basic DDI process, the contextualized DDI alerts were triggered in batches at 06:00, 09:00, 11:00 and 15:00 and evaluated between 08:00 and 17:30. For the prescribers the MO process was not changed during the study i.e. basic DDI alerts were also directly presented to the prescriber. DDI alerts triggered using the contextualized DDI-CDS system were evaluated by the hospital pharmacist. Preliminary alert evaluation by a pharmacy technician was omitted and mostly replaced by the contextualized DDI-CDS system. Table S1 provides a complete list of CDS evaluations replacing pharmacy technician evaluations. Absorption time-dependent DDI alerts were shown only to the pharmacy technician; the correctness of the adjustments made by the pharmacy technician was checked by the contextualized DDI-CDS system in the first following batch.

CONTEXTUALIZED DDI SPECIFICS: ALERT CONTEXTUALIZATION AND SUPPRESSION

Basic as well as contextualized DDI-CDS systems used the Dutch G-standard knowledge base content, which includes DDI assessments used nationally in the Netherlands.[44] During the study, the knowledge base was updated monthly, following a regular schedule. As of November 2020, G-standard knowledge base contained 1058 DDIs, incorporating a total of 32,676 drug pairs. A drug pair was defined as Anatomical Therapeutic Chemical code (ATC) A + ATC B.

In addition to basic suppression (turning a specific alert off), the contextualized DDI-CDS system combined two overarching types of alert contextualization and alert suppression. The first type being suppression based on the workflow context, the second being suppression based on the clinical context. Workflow suppression included 1) suppression based on previous DDI alert evaluation (i.e. DDI alerts only reappeared if medication and daily dose were changed, changing from 'if necessary use' to regular use or from 'one time use' to regular use were defined as dose changes), 2) suppression based on previously unevaluated DDI alerts and 3) suppression based on the ATC codes of drugs appearing in multiple MOs (e.g. haloperidol 10 mg + 1 mg + amiodarone 200 mg clustered to show a single alert for haloperidol with amiodarone).

General clinical context suppression, performed on all DDI alerts, included suppressing DDI alerts where one of the drugs was already stopped at the time of showing the DDI alert. DDI alerts including stopped cytochrome P450 (CYP) inhibitors with long half-life and CYP inducers however were shown; full list of included inhibitors and inducers is included at the bottom of table 2.

Table 2 shows the contextual modulators used for suppression based on clinical context. In total 15 different types of contextual modulators were used for specific suppression of DDI alerts, grouped into five major contextual modulators.[27] Specific clinical context suppression spanned out over 93 out of the total 1058 DDIs, including a total of 8,739 drug pairs using 11,627 modulators. This included basic DDIs previously overlapping clinical rules which could be turned off for pharmacy staff in its entirety. Table S1 provides details on all meta-rules applied.

Contextualized DDI alerts presented additional contextual information to pharmacy staff. The information provided was based on recommendations by Payne *et al.*[40] Figure S1 panel D gives an example of a contextualized DDI alert.

TABLE 2. *The types of clinical context suppression, including examples, applied in this study.*

Clinical context suppression based on modulator: (number of drug pair combinations [a] to which the modulator was applied) [b]	**Explanation** (example)
Prescription of interaction drug pair (3,591)	
Dose (152)	Suppression when DDI was not applicable for a specific dose *e.g. simvastatin ≤ 40 mg combined with ticagrelor*
Route of administration (94)	Suppression when DDI was not applicable for a combination of drugs using different routes of administration *e.g. midazolam nasal spray combined with verapamil*
Chronology and lag time between administrations [f] (1318)	Suppression when drug administration times were sufficiently spaced to prevent absorption DDI *e.g. ciprofloxacin at 08:00 and 20:00 combined with calcium at 15:00*
No alternative available (275)	Suppression when no therapeutic alternative was available in the setting *e.g. labetalol intravenous combined with insulin intravenous*
Course of therapy (1,752)	
'Only' If necessary use (127)	Suppression when drug use was used once or only used if necessary *e.g. haloperidol if necessary < 5 mg combined with amiodarone*
Short duration of administration (45)	Suppression when drug combination was present only for a short duration, including once *e.g. verapamil 2.5 mg once during percutaneous coronary intervention combined with digoxin*
Drug-drug combination existing prior to admission (1,580)	Suppression when DDI existed prior to admission *e.g. metoprolol combined with paroxetine*
Drug pair combination stopped [c] (all) (General rule)	Suppression when one of the drugs was already stopped [c] e.g. starting mirabegron while metoprolol was previously stopped
Co-medication (4,033)	
Pharmacodynamic counter-DDI (828)[c]	Suppression when DDI increased risk is mitigated by co-medication [c] *e.g. naproxen and dexamethasone when pantoprazole was co-administered*
Pharmacodynamic risk modifiers (e.g. DDIs only relevant in case multiple drugs involved) (3205)	Suppression when only two of the three drugs increasing the risk of clinically significant DDI were present *e.g. perindopril combined with furosemide with ibuprofen already in use*
Patient characteristics (1,663)	
Patients age (835)	Suppression when DDI was only applicable to a certain age category *e.g. ceftriaxone intravenously administered combined with calcium-containing intravenous fluid in patients > 1 month old*
Comorbidity (828)	Suppression when DDI was only applicable combined with comorbidities *e.g. naproxen + dexamethasone in patient of 30 years with previous gastric ulcer*
Dynamic patient information (2,311)	

Clinical context suppression based on modulator: (number of drug pair combinations [a] to which the modulator was applied) [b]	**Explanation** (example)
Lab results (1833)	Suppression when laboratory value monitoring was ordered or result was known *e.g. hydrochlorothiazide combined with citalopram when sodium was ordered*
Vital signs (478)	
Actual measurements (9)	Suppression when vital signs where above or below certain values *e.g. metoprolol + fluoxetine and heart rate > 60 beats per minute*
Routine monitoring [f] (469)	Suppression when routine monitoring was performed *e.g. alpha-blocker combined with beta-blockers on all medical wards*
Deemed not clinically relevant in all cases (2)	
Clopidogrel + (es)omeprazole	Suppression of a specific DDI rated not clinically relevant

Contextual modulators which were used for suppression as described by Seidling *et al.* 2014. were applied.[27] Grouping modulators are shown in grey rows. (sub)Modulators, presented in italic type in the left hand column, were added to an existing modulator or modulator group. Several contextual DDI alerts showed different content or advice dependent on contextual modulators. The number of contextual modulators includes modulators used in the clinical rules in use previous to the study.

[a] Definition of a single drug was done based on Anatomical Therapeutic Chemical (ATC) code. A drug pair was therefore defined as ATC A + ATC B; e.g. N06AB03 (fluoxetine) + C07AB02 (metoprolol)
[b] Multiple contextual modulators could be applied to a single drug pair. (e.g. N06AB03 (fluoxetine) + C07AB02 (metoprolol) e.g. drug combination used prior to hospitalization and routine monitoring (continuous cardiac monitoring if admitted to ICU)
[c] A general rule applied to all drug pairs was used to suppress all DDI alerts where one of the drugs from the drug pair was already stopped excluding pharmacokinetic interactions [d] relevant after stopping (e.g. amiodarone stopped one day before starting digoxin)
[d] Drugs (perpetrators) included as relevant after stopping included cytochrome P450 (CYP) inhibitors with long half-life: hydroxychloroquine (100 days), chloroquine (28 days), fluoxetine (15 days) and amiodarone (150 days) and CYP inducers (28 days): rifampicin, primidone, phenytoin, phenobarbital, carbamazepine, efavirenz, hypericum and ritonavir.
[e] Previous to the current study clinical rules were already in use monitoring ordering of timely therapeutic drug monitoring when applicable, drug induced electrolyte disorders or electrolyte disorders without proper drug management, International Normalized Ratio (INR) monitoring and use of gastric protection dependent of multiple risk factors including patients' age, pharmacodynamic DDIs and monitoring including pharmacodynamic counter-DDI. Table S1 (bottom) includes a full list of drug-pairs included including contextual modulators used.
[f] Routine monitoring modulator included advice to monitor heart rate and blood pressure on regular wards and DDI alerts advising electrocardiography (ECG) on wards that performed continuous cardiac monitoring. These wards included intensive care unit (ICU), cardiac medium care unit (MCU) and cardiac lounge.
DDI: drug-drug interaction; ATC: Anatomical Therapeutic Chemical

CLINICAL UTILITY

Four outcome measures were used to determine clinical utility for both CDS management processes, namely:

1. Positive predictive value (PPV) of the DDI alerts shown

An alert was considered to be a true positive (TP) if found to be clinically relevant. Clinical relevance in context of this study was defined as an alert intervened upon by a pharmacy professional. DDI alerts not considered clinically relevant were counted as false positives (FPs). PPV was calculated as TPs / (TPs + FPs). PPV was calculated for the basic and contextualized DDI phases.

2. Negative predictive value (NPV) of the DDI alerts shown

Pharmacy interventions not shown in the background data collection were considered false negatives (FNs). The remaining DDI alerts not shown in the background data were considered true negatives (TNs). Hence, NPV was calculated as TNs / (FNs +TNs). The NPV was calculated only for the basic phase.

3. Number of pharmacy interventions (PIs) /1,000 medication orders

Pharmacy interventions (PIs)/1,000 medication orders was calculated using the total number of PIs in a phase dived by the total number of included MOs for that phase times a 1000. Pharmacy interventions were included if registered as such in the EHR or the CDS system.

4. Time spent on DDI management /1,000 medication orders

The time measurements needed for all separate steps of the DDI management process in the basic as well as contextualized DDI phase was measured for MOs with DDI alert using a stopwatch. MOs with DDI alerts were measured. If multiple DDI alerts appeared on one MO, the total time spent evaluating the MO was measured, and the number of DDI alerts was noted and total time spent on the MO was divided by the number of DDI alerts noted.

Total time spent on DDI management in basic and contextualized DDI phase was the addition of the median time of each step of the DDI management process multiplied by the frequency of occurrence. This was done separately for absorption time-dependent DDIs and remainder of the DDIs; irrelevant and relevant DDI management evaluation were also measured.

DATA ANALYSIS

Statistical tests were performed using SPSS v 27.0.0. A Mantel-Haenszel test to test for difference in frequency in the number of DDI alerts /1,000 MOs triggered and shown.[45] An additional Bonferroni correction was used to test for the difference in DDI alerts shown for the different medical specialties. A general estimation of equations (GEE) was used to test the difference in PPV between both methods.[46] A two proportion Z-test was used to test the difference in number of pharmacy interventions (PIs)/1,000 medication orders.[47] A p-value of <0.05 was considered statistically significant. No statistical comparison was done to compare time spent on DDI management per 1,000 medication orders.

RESULTS

MEDICATION ORDER INCLUSION AND DDI ALERT CHARACTERISTICS

The basic DDI phase (35 days) included 67,188 MOs with 14,787 triggered basic DDI alerts

belonging to 1,528 patients, i.e. a mean of respectively 1,920 MOs/day and 423 triggered basic DDIs alerts/day. The contextualized DDI phase (50 days) included 92,659 MOs triggering 22,626 basic DDI alerts (in the background) belonging to 2,077 patients, i.e. a mean of respectively 1,853 MOs/day triggering 453 basic DDI alerts/day. Surgery patients accounted for most of the triggered DDI alerts, 4,764 (32%) and 6,647 (29%) of the basic and contextualized DDI phases, respectively. Table S2 shows DDI alert characteristics top 30 of both phases. Most triggered DDI alerts were of drugs increasing the risk of gastric ulcers (approx. 30%), DDIs involving CYP/P-glycoprotein/uridine diphosphate glucuronosyltransferase followed (approx. 18%) and time-dependent absorption DDIs (approx. 15%). There was no substantial difference in the number of triggered basic DDI alerts/1,000 MOs; 220 and 244 for the basic and contextualized DDI phase respectively. There were no statistical differences in respect to patients age, gender, treating specialty and number of drugs used at hospitalization between both phases.

CLINICAL UTILITY

Comparing basic DDI management process to contextualized DDI management in the basic DDI phase

The left-hand side of Table 3 presents the results of the basic DDI phase for both DDI-CDS systems, including the differences. During this phase, 3,835 DDI alerts were shown to pharmacy staff using the basic DDI-CDS system, leading to 107 interventions, resulting in an overall PPV of 2.8%. Using the background data, the contextualized DDI-CDS system would have shown 498 DDI alerts, resulting in a reduction in displayed DDI alerts of 88.1%, compared to the basic DDI-CDS system, which would have resulted in a PPV of 23.5% (107/456). Seven of the 107 relevant alerts were not triggered by the contextualized DDI-CDS system because they had been resolved before starting the batch run. Assuming these seven alerts would have been triggered without previous intervention, no relevant alerts were likely to have been missed in the contextualized DDI-CDS system, resulting in a 100% NPV.

Comparing the contextualized DDI-CDS system to the basic DDI-CDS system in the contextualized DDI phase

The right-hand side of Table 3 presents the results of the contextualized DDI phase for both DDI-CDS systems. During this phase, 902 DDI alerts were shown to pharmacy staff using the contextualized DDI-CDS system, leading to 373 interventions, resulting in an overall PPV of 41.4%. The basic DDI-CDS system would have shown 5,824 DDI alerts of which 363 could have led to an intervention, as 10 alerts were suppressed using basic suppression. Background data collection PPV was 6.3%. The difference in PPVs between both systems was 38.6%, $p < 0.01$.

TABLE 3. *A comparison of basic DDI-CDS alerts and contextualized DDI-CDS alerts for both DDI phases.*

	Basic DDI phase (35 days)				**Contextualized DDI phase (50 days)**					
	Basic DDI-CDS system	***Contextualized DDI-CDS system***	Difference between systems		***Basic DDI-CDS system***	**Contextualized DDI-CDS system**	Difference between systems		Difference between phases **in clinical practice**	
	Clinical practice	***Background data collection***	Change	p-value	***Background data collection***	Clinical practice	Change	p-value	Change	p-value
Absolute results										
MOs	67,188		n/a	n/a	92,659		n/a	n/a	n/a	n/a
Basic DDI alerts triggered	14,787		n/a	n/a	22,626		n/a	n/a	n/a	n/a
DDI alerts shown	3,835[c]	*456*	n/a	n/a	*5,824*[c]	902	n/a	n/a	n/a	n/a
Pharmacy interventions	107	*107*[a]	n/a	n/a	*363*[b]	373	n/a	n/a	n/a	n/a
Normalized results										
Basic DDI alerts triggered /1,000 MOs	220.1		n/a	n/a	*244.2*		n/a	n/a	+10.9%	n/a
DDI alerts shown /1,000 MOs	57.1	*6.8*	*-88.1%*	< 0.01	*62.9*	9.6	*-84.1%*	< 0.01	-83.1%	< 0.01
PPV	**2.8%**	*23.5%*	+20.7%	< 0.01	6.3%	**41.4%**	+35.1%	< 0.01	**+38.6%**	**< 0.01**
NPV	n/a	***100%***	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
PIs/1,000 MOs	1.6	n/a	n/a	n/a	n/a	4.0	n/a	n/a	**+250%**	**< 0.01**
Median time spent on DDI management /1,000 MOs	**(37.2 min.) 2233.3 sec.**				**(13.7 min.) 821.9 sec.**				**-63.2%**	n/a

In both phases, DDI alerts from the basic DDI-CDS system and the contextualized DDI-CDS system are shown. DDI alerts shown in clinical practice are presented in black font; those from the background data collection are shown in grey italic type. The outcome measures used to assess clinical utility are presented in bold font.
[a] Of the 107 DDI alerts with intervention in the basic DDI phase, seven would have been revealed by the contextualized DDI-CDS system; however, DDIs were resolved before starting the contextualized DDI-CDS system batch run.
[b] Ten DDI alerts were suppressed using basic suppression and were therefore unavailable for intervention in the basic DDI-CDS system (triple HIT [RAAS + diuretic + NSAID] *n* = 9, beta-blocker + antidiabetic *n* = 1).
[c] Only a portion of the basic DDI alerts triggered were shown to prescriber as well as pharmacy staff: 14,787 DDI alerts were triggered in the basic DDI phase and 22,626 alerts were triggered in the contextualized DDI phase. Most DDI alerts were not shown based on national assessment of clinical relevance 44.
DDI: drug-drug interaction; CDS: clinical decision support; MOs: medication orders; n/a: not applicable; PPV: positive predictive value; NPV: negative predictive value; RAAS: renin-angiotensin-aldosterone system; NSAID: nonsteroidal anti-inflammatory drug

Comparing clinical practice between phases

A significantly higher PPV of 41.4% was achieved during the contextualized DDI phase, compared to 2.8% during the basic DDI phase, $p < 0.01$. The same was true for the number of PIs/1,000 MOs, 24.6 during contextualized DDI phase compared to 9.9 in basic DDI phase, $p < 0.01$. The number of PIs was higher for all types of DDIs. Total time spent on DDI management /1,000 MOs was reduced from 37.2 minutes in basic DDI management phase to 13.7 minutes in contextualized DDI management phase. For pharmacy technicians, the median time spent performing DDI management /1,000 MOs was reduced from 23.6 min in the basic DDI phase to 9.0 min in the contextualized DDI phase. For hospital pharmacists this was 13.7 min in the basic DDI phase and 4.7 min in contextualized DDI phase. Table S3 shows the median time spent on DDI management in both phases, based on actual practice and stratified according to healthcare professional.

Contribution of different suppression techniques during contextualized phase

During the contextualized DDI phase, workflow suppression made the most significant contribution to DDI alert suppression (38.9%, $n = 42,766$), the highest contribution (98.4%) of the previously evaluated DDI alerts. During the same phase, 10,686 unique DDI alerts were suppressed using clinical context suppression. Ignoring workflow suppression, pharmacy technician context suppression would have suppressed 67.9% ($n = 36,402$) of all triggered DDI alerts by the contextualized DDI-CDS system. The most significant contributions to suppressed alerts were 1) No alternative available in a hospital setting (30%), 2) pharmacodynamic risk modification; three-way DDIs involving only two drugs (24.6%) and 3) lag time between administrations in absorption time-dependent DDIs (18.0%).

DISCUSSION

PRINCIPAL FINDINGS

This study demonstrated that contextualized DDI management has greater clinical utility than basic DDI management regarding hospitalized patients in a clinical pharmacy setting. Clinical utility improved in all the outcome measures; PPV was 35.3% higher in the contextualized DDI management process, and NPV was 100% for the contextualized DDI-CDS system. Furthermore, the number of PIs increased from 1.6/1,000 MOs with basic DDI management to 4.0/1,000 MOs with contextualized DDI management; suggesting a high degree of alert fatigue with basic CDS-DDI management.

COMPARISON OF THIS RESEARCH TO OTHER STUDIES

Several previous studies have shown that adding clinical and or workflow context can significantly reduce the DDI alert burden. Helmons *et al.* and Daniels *et al.* reduced the

number of alerts by approximately 50%.[12,33] Improvement in PPV was also demonstrated i.a. Eppenga *et al.* increasing from 9.9% to 14.8% after introducing a contextualized DDI-CDS.[32,35] While all previous studies find improvements in reduction of DDI alerts, the effect size in reduction of DDI alerts (93%) and achieved PPV (41.4%) achieved in this study have not been demonstrated before. Moreover, this study shows that this PPV improvement can be achieved without sacrificing NPV (100%). No previous studies were found showing that decreasing the number of DDI alerts shown to pharmacy staff actually increases the number of pharmacy interventions. Moreover, this was done concurrently with a considerable time reduction to pharmacy staff (37.2 to 13.7 min/1,000 MOs).

STUDY LIMITATIONS

An obvious limitation of the study was the research design being non-randomized and open-label to pharmacy staff and only performed in clinical pharmacy setting. A cross-over design can be sensitive to seasonal and healthcare professional influences. However, in this case the crossover design provided data for both periods using both systems, making this possible influences insightful. The rate of DDIs triggered/1,000 MOs as well as the number of displayed DDIs/1,000 MOs was different between the two phases. However, the rate was higher in the contextualized DDI phase, making the measured difference in clinical utility an underestimation rather than an overestimation. Furthermore, the process change was studied in one hospital and used one EHR. Nonetheless, adopting a similar approach and using the same contextualized DDI-CDS system, researchers investigating different EHRs have obtained similar results[33]. The study could also be subject to researcher bias as three of the authors were also hospital pharmacists (in training) performing DDI management in both phases. Nevertheless, these were only three of the 16 members of the hospital pharmacy staff and none had any conflicts of intertest.

A technical limitation was that the contextualized DDI process triggered DDI alerts in batches, which could, in theory, leave patients vulnerable to DDIs as pharmacy interventions are not timely performed. However, compared to basic DDI management practice, hospital pharmacists received DDI alerts sooner, as there was no delay in pharmacy technician evaluation. To enhance clinical utility for prescribers, it is necessary to perform this contextualized DDI alerting in real-time. Fortunately, this is currently possible and is already being used in several other hospitals across the Netherlands. Another limitation of the study was that there was no expert review of DDI alerts to assess NPV. In clinical practice, however, staff and time constraints inhibit the expert review of each DDI alert. Using PIs in clinical practice resulted in an NPV of 100% under the contextualized DDI management process.

CONSIDERATIONS FOR CURRENT PRACTICE AND FUTURE IMPROVEMENTS

This study shows that significant decrease in DDI burden can been achieved by using a simple contextual modulators. Based on this study additional more sophisticated contextual

modulators don't seem to be a top priority for a general hospital setting. Analysis of the residual FPs also showed that many FPs could be traced back to workflow-related technical issues. Most of which were resolved by implementing an auto-refresh function and waiting for the CDS to display the alert after all meta-rules had been executed. Gaston Pharma® has been shown to be easily combined with different knowledge bases and providing contextualized CDS linked to several different CPOEs and/or EHRs.

The greatest benefit as it comes to time savings in the current study was removing the pharmacy technician from the primary DDI alert evaluation on non-absorption time dependent DDIs and replacing them by the contextualized CDS system and the other way around for absorption time dependent DDIs.

Basic pair-wise DDI-CDS systems in hospital practice are common in Western countries.[21,30,48] In the Netherlands, CPOE including basic pair wise DDI-CDS is mandatory in all medical settings as off the 1st of January 2014. No references have been found using a contextualized CDS-DDI system in clinical practice on a larger scale. Since October 2020, the Netherlands has however moved its DDI knowledge base from a pair-wise combination model to a decision tree model, comparable to the models used in this study. Thus, enabling all healthcare providers to benefit from contextualized DDI management in a clinical context. However, it is important to consider that the greatest percentage of suppression during this study was achieved by workflow context suppression. Therefore, consideration should also be given to if and how to deploy and implement workflow contextualization improvements.

CONCLUSION

Contextualized DDI management compared to basic DDI management in a clinical pharmacy setting can considerably decrease the number of irrelevant DDI alerts and thereby increase the time available to interpret relevant DDI alerts leading to more relevant interventions without missing relevant DDI alerts.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found at:
https://ascpt.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fcpt.2624&file=cpt2624-sup-0001-SupinfoS1.docx

Or by scanning the QR code:

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CHAPTER 2.2

Identifying adverse drug reactions from free- text electronic hospital health record notes

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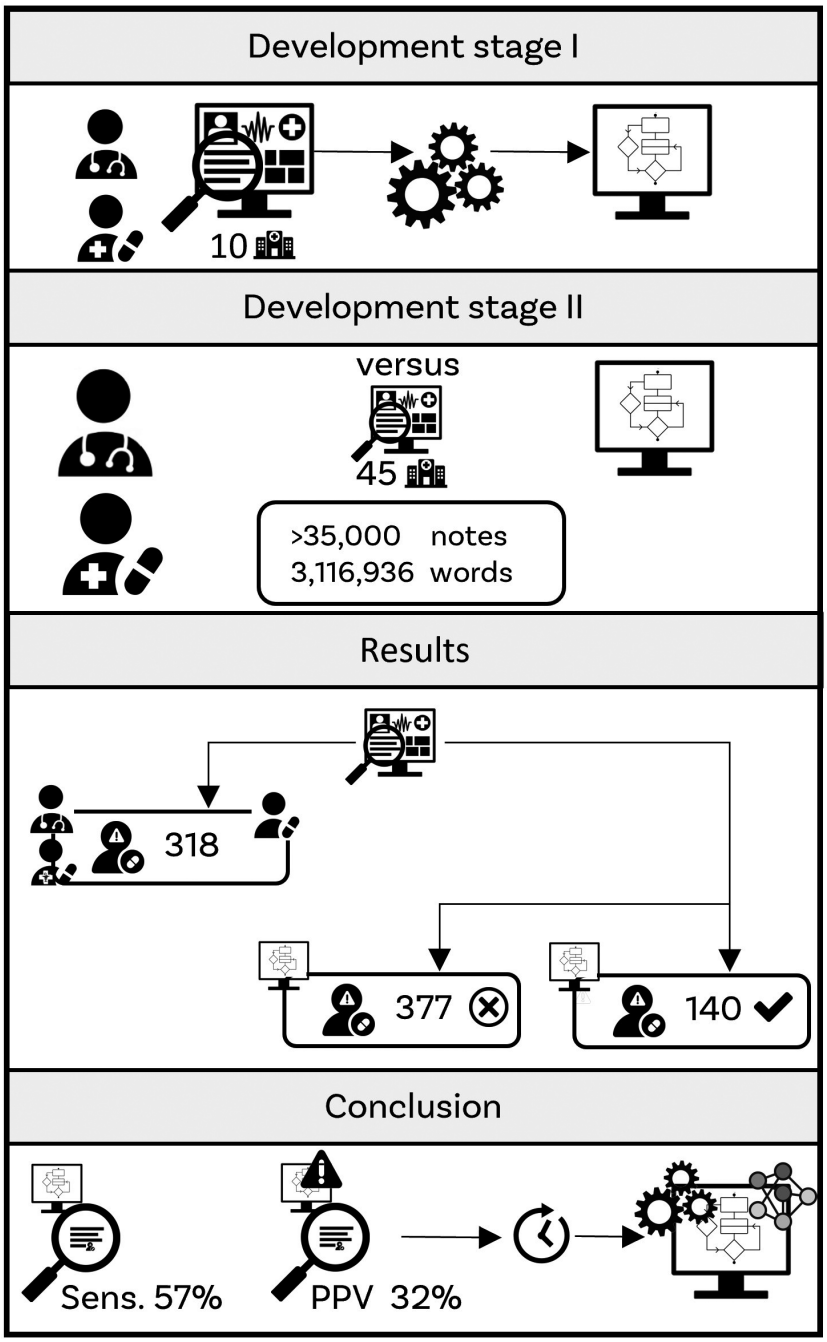
GRAPHICAL ABSTRACT



ABSTRACT

BACKGROUND

Adverse drug reactions (ADRs) are estimated to be the fifth cause of hospital death. Up to 50% are potentially preventable, and a significant number are recurrent (reADRs). Clinical decision support systems have been used to prevent reADRs using structured reporting concerning the patient's ADR experience, which in current clinical practice is poorly performed. Identifying ADRs directly from free-text in electronic health records (EHRs) could circumvent this.

AIM

to develop strategies to identify ADRs from free-text notes in electronic hospital health records.

METHODS

Stage I, the EHRs of ten patients were reviewed to establish strategies for identifying ADRs. Stage II, complete EHR histories of 45 patients were reviewed for ADRs and compared to the strategies programmed into a rule-based model. ADRs were classified using MedDRA and included into the study if the Naranjo causality score was ≥1. Seriousness was assessed using the European Medicine Agency's important medical event list.

RESULTS

Stage I, two main search strategies were identified: keywords indicating an ADR and specific prepositions followed by medication names. Stage II, EHRs contained a median of 7.4 (range 0.01–18) year's medical history covering over 35,000 notes. A total of 318 unique ADRs were identified of which 63 potentially serious; 179 (sensitivity 57%) of those were identified by the rule. The rule falsely identified 377 ADRs (PPV 32%). However, also identified an additional eight ADRs.

CONCLUSION

Two key strategies were developed to identify ADRs from hospital EHRs using free-text notes. The results appear promising and warrant further study.

INTRODUCTION

Adverse drug reactions (ADRs), including allergic responses, frequently occur and significantly influence morbidity, mortality, and medical costs[1,2]. About 3.6–6.5% of hospitalizations are related to an ADR.[3-7] Furthermore, 10–15% of patients develop an ADR during hospitalization[4,8] resulting in death in 0.05–0.25% of cases[4,9]. Adverse drug reactions are the fifth cause of hospital deaths.[4,10] Moreover, 28–56% of all ADRs are potentially preventable.[5,7,11,12] Different approaches have been used to define preventability, and most of these presenting difficulties for translation into interventions. A significant number of potentially preventable ADRs are recurrent ADRs (reADRs) (10–30% of all ADRs[13,14], 13–50% of medication-related hospitalizations[14-17]). Recurrent ADRs have a different form of preventability compared to first occurrence ADRs, introducing knowledge on a patient's response to a drug in a certain dose in a certain context making them easier to prevent. Preventable reADRs have multiple origins. The most important cause is unintended represcription, defined as the represcription of medication previously intentionally stopped due to an adverse drug reaction (e.g., the represcription of hydrochlorothiazide stopped due to hyponatraemia in an elderly woman).[15,18] To prevent unintended represcriptions and the risk of reADRs, clinical decision support systems (CDSSs) have been implemented to alert prescribers when a medication is represcribed after it was previously stopped due to an ADR.[19] Currently, however, CDSSs only function when the ADR is registered as structured information at the level of the individual patient within an ADR module linked to or part of the computerized physician order entry (CPOE) system of the electronic health record (EHR). In current clinical practice, this is poorly performed due to time constraints, inadequate IT systems, a lack of peer support and failing to acknowledge the importance of structurally registering ADRs.[20] Healthcare professionals frequently describe ADRs in clinical notes and discharge summaries, using free-text entries[18], that are not effective in preventing unintended represcription.[16,21,22]

Identifying ADRs directly from free-text EHR notes could solve the issue of underreporting in a structured format by healthcare professionals. In recent years, progress has been made in identifying ADRs from free- text. Honingman *et al.* developed an algorithm to screen primary care records[23]. Iqbal *et al.* developed and validated an algorithm to detect specific ADRs related to antidepressants and antipsychotics in psychiatric hospital EHRs.[24] Aramaki *et al.* developed and tested an ADR identification algorithm using Japanese discharge summaries.[25] The sensitivity of the different algorithms was approximately 60% for general ADR identification[23,25] and up to 90% for specific ADRs[24].

Previous studies have focused on specific medication[24,26], specific ADRs[27,28], selected notes[25,28-36], and specific settings[23,24]. No studies have been identified that use a general approach to detect ADRs from all free-text available in a hospital EHR system. Investigating specific notes may result in identifying only a fraction of the reported ADRs; focusing on specific ADRs automatically overlooks other ADRs. Moreover, previous studies have not

assessed causality and seriousness of the identified results. Therefore, the aim of this study was to develop strategies to identify ADRs from free-text notes in electronic hospital health records.

METHODS

DESIGN AND SETTING

The study was performed at the Catharina Hospital, Eindhoven, The Netherlands, a 696-bed teaching hospital that used CS-EZIS® (version 5.2, Chipsoft B.V. Amsterdam) for its EHR system. This EHR system was implemented in stages, launching in 2008 and adopting paperless recording from 2015 onwards. Medical records before 2008 are available (as scanned PDF) as part of the multimedia module. Within the EHR system there are distinct modules. For example, a CPOE module, a module for structured ADR registration, a CDS system module and a module for free-text EHR notes. Inside the free-text EHR module, different types of EHR notes may be distinguished (e.g., physician notes, nursing notes, pathology notes, radiology notes and operation notes). An EHR note is registered at a specific time and could contain multiple entries such as medical history, physical examinations, additional findings, summaries, and therapeutic plans. Figure 1 provides a graphical representation of the EHR structure. To supply additional, medication-related, clinical decision support, the hospital uses Gaston Pharma® (Gaston Medical®, Eindhoven), which is linked to the EHR database.

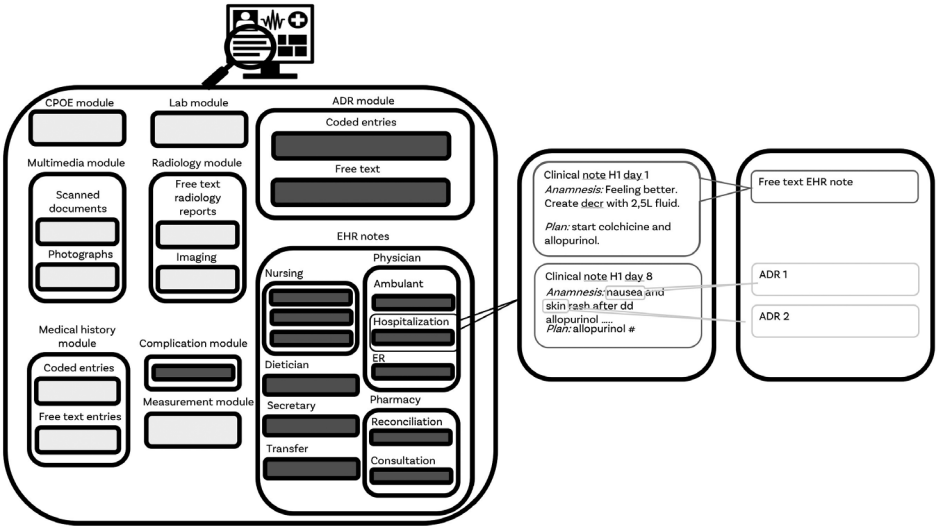


FIGURE 1. *On the left is a graphical representation of the EHR including the different modules. The free-text notes included from the different modules are marked grey. On the right is an example of a free-text EHR note with two potential ADRs.*

STAGE I - IDENTIFICATION OF SEARCH STRATEGIES

To discover strategies for identifying ADRs, the EHRs of ten random patients from internal medicine and geriatric departments were manually screened and supplemented with strategies devised by the researchers. Adverse drug reactions retrieved from the manual review were categorized into key identification strategies. These were subsequently fine-tuned by adding different words with the same meaning, commonly used abbreviations for these words, and typing and common spelling errors. Based on the false negatives, letter combinations or text strings were identified which were to be ignored, followed by variations, abbreviations, typing, and spelling errors. The strategies were programmed into a rule-based model using the available CDS system, Gaston Pharma®. The model output included a text string containing the identified keywords (determined by the strategy), the entire free-text EHR note, and the EHR notes without the disregarded text strings. One output could contain one or more ADRs.

STAGE II - INCLUSION OF PATIENTS' ELECTRONIC HEALTH RECORDS

Performance of the rule-based model was assessed using 45 additional EHRs, which were compared to a manual EHR review. The EHRs of 45 consecutive patients were included in the study when the patients were hospitalized for over 24 hours to either the department of geriatrics (15), internal medicine (15), or oncology (15). The inclusion order was based on reverse chronological discharges before June 1, 2018. A complete history of the free-text EHR notes was included. Scanned or imported (PDF) documents were excluded.

STAGE II – ELECTRONIC HEALTH RECORD REVIEWS, DEFINITIONS, AND CLASSIFICATION

The manual EHR review was performed independently by two assessors (a clinical pharmacist and a physician in training) using a predefined protocol, included in supplement I. The EHRs were searched for free-text notes containing potential ADRs. The ADRs were defined according to the World Health Organization (WHO): "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function".[37] Type A-D potential ADRs were included; ADR type A): augmented pharmacological effects, type B): bizarre, including allergic and nonimmune drug sensitivities, type C): chronic effects and type D): delayed effects, including carcinogenesis and teratogenesis.[38] In cases where the two assessors did not reach a consensus, a third assessor (a member of the Dutch Pharmacovigilance Centre LAREB) gave the final decision. Symptoms or diseases with multifactorial causes, including medication, were included as potential ADRs (e.g., 'hyponatraemia due to malnutrition and hydrochlorothiazide use.') Duplicate entries (i.e., the same ADR occurring during the same hospitalization) were not included. Recurrent ADRs were scored separately. An ADR was considered recurrent if the medication was represcribed, or the ADR occurred during

a separate hospitalization. Free-text and CPOE were not searched to find out if special measures were taken to modify risk of recurrence when represcribed (e.g., dose reduction). Anatomical Therapeutic Chemical (ATC) classification was used to code the medication associated with the ADR. An ADR having more than one medication as the possible cause was included as a single ADR with all separately coded medications. In contradiction to pharmacovigilance requirements, ADRs without specific drug names mentioned however with a drug group mentioned (e.g., hyponatraemia due to antidepressant use), were included into the study, as these can still present important additions to the care process and medical history. The rule-based model used the Dutch G-standard database, including all generic medicine names, trade names, and group names registered in the Netherlands.[39] The ADRs were classified using the Medical Dictionary for Regulatory Activities (MedDRA® version 23.1). MedDRA® provides validated standardized hierarchical structure terminology, which is used by regulatory authorities, post-marketing pharmacovigilance institutes, and pharmaceutical manufacturers. The ADRs were classified using the lowest hierarchy, being the lower-level term, while the preferred term, used in the summary of product characteristics (SmPC), was matched to obtained references to ADRs. For example, the lower-level terms *tingling of extremity*, *pins and needles*, and *peripheral neuropathy* all fall within the preferred term *paraesthesia*. ADRs were categorized as potentially serious using the corresponding European Medicines Agency's Important Medical Events list.[40] The causality of the ADRs was assessed by a clinical pharmacist trained in pharmacovigilance using the Naranjo algorithm. Only ADRs with a Naranjo score of ≥ 1 were included.[41]

STAGE II - DATA COLLECTION

At the moment of hospitalization, characteristics such as gender, age, total medications (including over-the-counter medications), and treatment specialisms were collected from the patients' EHRs. Medical history and laboratory results were collected to calculate Charlson Comorbidity Index. Moreover, the following information was collected to characterize the data: the number of hospitalizations (≥ 24 hours) and ambulant visits (including hospitalizations < 24 hours), medical specialisms, record history, the number of EHR notes, and the number of words (calculated using spaces) and characters used. The following data was collected for each EHR note containing ADRs: ADRs, medication involved, search strategy, surrounding paragraph or context (including the space between words, date, form, and type of healthcare professional). Research Manager® (Cloud9, Deventer) was used to record, edit, and save the anonymized data. Venn diagram plotter version 1.5.5 was used to construct the Venn diagram.

STAGE II - DATA ANALYSIS

If an alert generated by the rule contained multiple ADRs, they were all considered to be identified. True positives (TPs) were ADRs identified by the manual and rule-based EHR

reviews. False positives (FPs) were identifications by the rule-based EHR review but not the manual review. False negatives (FNs) were ADRs not identified by the rule-based EHR review. Sensitivity was calculated as TPs / (TPs + FNs). The positive predictive value (PPV) was calculated as TPs / (TPs + FPs). False negatives and FPs were further analyzed to improve the applied search strategies and search for additional strategies to improve future versions of the tool. False positives were also analyzed to provide recommendations for improving the list of disregarded text strings and context.

RESULTS

STAGE I - IDENTIFICATION OF SEARCH STRATEGIES

Based on the ten EHR records, five key strategies for identifying EHR notes containing ADRs were identified (Table 1). Table S1 provides a full overview, including disregarded text strings and original Dutch words. The first strategy (S1) used keywords implying one or multiple ADRs, including conjugations of a) drug-induced, b) allergy, c) side-effect, d) intolerance, e) reaction, and d) toxicity. The second strategy (S2) included a search of thirteen different prepositions followed by drug groups, names, therapies, or their abbreviations. An example could be "pins and needles after FOLFOX cycle." Table S1 provides a full list of the added abbreviations used in S1 and S2. The third strategy (S3) used free-text entries titled *allergy* and *anaphylaxis*. Such free-text entries were used when the ADR module was introduced in 2015. The fourth strategy (S4) searched the complication registration module for drug-related complications. The final strategy (S5) searched for ADRs registered in the ADR module, including coded and free-text entries.

STAGE II – PATIENT AND DATA CHARACTERISTICS

Table 4 presents the patient and data characteristics included in the 45 EHRs. The mean age of the patients was 68 years (range 21–92), and 64.4% were female. During the most recent hospitalization, patients had a median Charlson Comorbidity Index score of five (range 0–13) and used a median of eight (range 0–20) different medications. Patients had a median of three hospitalizations (range 1–39) and 60 ambulant visits (i.e., hospital stay < 24 hours) (range 2–433), resulting in a median medical history of 7.4 years (range 0.01–18). The median number of free-text EHR notes per patient was 585 (range 41–2,820). These were formed of a median of 41,921 words (range 4,070–259,750) constructed by a median of 449,179 (22,027–2,594,750) characters. This resulted in approximately 35,000 free-text EHR notes for review.

TABLE 1. *Summary of ADR identification strategies used in the rule.*

Nr.	Search strategies		Included trigger words++
S1	Keywords implying an ADR	conjugations of	drug-induced allergy side-effect intolerance toxicity reaction
S2a	Prepositions followed closely* by a drug group*, a generic drug name, a drug brand, trade name or abbreviation a drug or drug therapy***	conjugations of	by with after of on since
S2b	Abbreviations using the included prepositions	conjugations of	a.r. (as a result) b.o. (based on) a.c.o. (as a consequence of)
S3	Content of forms labeled+	conjugations of	allergies: anaphylaxis:
S4	Content of complication registration containing key field drug-induced	-	-
S5	Content of ADR module	-	-

* The maximal number of characters between the preposition and the drug name was 16.
** The drug group names were based on the ATC therapeutic subgroup, pharmacological subgroup, chemical subgroup, or chemical substance (i.e., 2nd to 5th levels of ATC main groups classified by WHO).
The maximum number of characters (i.e., proximity, between a preposition and a drug name) was set at sixteen.
*** Examples being PPI (proton-pump inhibitor), HCTZ (hydrochlorothiazide), FOLFOX (combination therapy of fluorouracil and oxaliplatin). A full list of abbreviations is provided in Table S2.
+ Forms labeled *allergy* and *anaphylaxis* using free-text entries were employed prior to the introduction of the ADR module in 2015.
++ English translations of the trigger words are presented here; Dutch trigger words are presented in Table S1.

TABLE 2. *Patient and data characteristics.*

Variable		Range
Mean age in years	68	21–92
Female (%)	29 (64.4)	n/a
Variable	**Median**	**Range**
Charlson Comorbidity Index at last hospitalization	5	0–13
Unique medication used at last hospitalization (n)	8	0–20
Hospitalizations+	3	1–39
Ambulant visits++	60	2–433
Medical record history (years)	7.4	0.01–18
FT EHR notes per patient	585	41–2820
Words+++ per patient	41,921	4,070–259,750
Characters per patient	449,179	22,027–2,594,750

+ Hospitalizations were > 24 hours; hospitalizations < 24 hours were included as ambulant visits.
++ Ambulant visits included telephone and video consultations.
+++ The number of spaces was used to estimate the number of words.

STAGE II - INCLUSION OF ADVERSE DRUG REACTIONS

Figure 2 provides a flowchart showing the inclusion of potential ADRs discovered during the manual EHR review. A total of 643 potential ADRs were identified. During matching, 39 potential reADRs were detected, the remaining potential ADRs (*n* = 269) were identified as duplicates. Excluding the duplicates and reADRs resulted in 326 unique potential ADRs. After excluding eight (*n* = 8) potential ADRs with a Naranjo score < 1, 318 unique ADRs remained.

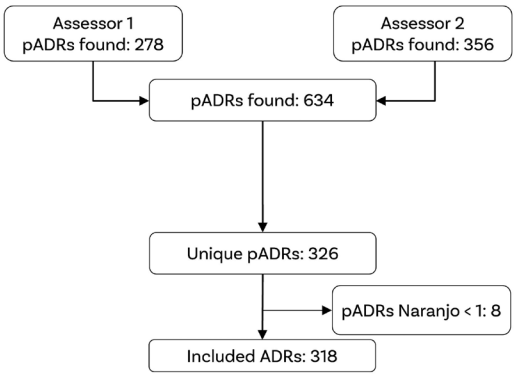


FIGURE 2. Inclusion and exclusion of potential ADRs.

pADRs: potential adverse drug reactions

STAGE II - TYPE OF ELECTRONIC HEALTH RECORD NOTES

Adverse drug reactions were found in different types of EHR notes. Most ADRs (68%, *n* = 216) were cited in physician notes, including ambulant, ER, and admission notes. However, 17% (*n* = 55) of the ADRs were only found in nursing notes. The remaining identified ADRs were only found in other types of EHR notes like dietician or pharmacist notes. ADRs included into the study were recorded by 206 individual healthcare professionals, dived over twelve medical specialisms.

STAGE II – ADVERSE DRUG REACTION CHARACTERISTICS

The median Naranjo score for the included ADRs was four (range 1-6). Fifteen ADRs were judged probable (score 5-8) and no ADRs were scored definite (score ≥ 9). Overall, patients had a median of four ADRs (range 0-32). The median number of ADRs was six (range 1-32) in the oncology EHRs and two (range 0-26) in the internal medicine and geriatric EHRs. Table S3 provides an overview of the number of ADRs per system organ class. A fifth (19.8%, *n* = 63) of all ADRs were classified as potentially serious, Table S4 provides an overview of all potentially serious ADRs and related medication. Twenty of those were related to chemotherapy, six to myelosuppression, seven to polyneuropathy, three to hepatotoxicity and one to a pulmonary embolism. Serious ADRs not related to chemotherapy were renal

failure (n = 6), myelosuppression (n = 5), hepatotoxicity (n = 4), and ileus (n = 2). Cardiac problems were frequently registered including bradycardia (n = 3), QT prolongation (n = 2), ventricular tachycardia (VT) (n = 1), and cardiovascular collapse (n = 1). One (n = 1) anaphylactic reaction and one (n = 1) case of allergic angioedema were also identified.

Most ADRs (87%, *n* = 278) were stated in the summary product characteristics (SmPC) of a causative medicine. Five percent (*n* = 14) could have been related to the ADRs cited in the SmPC, albeit not at the preferred term level, 3% (*n* = 10) of symptoms had no specific drug mentioned in the ADR entry, so no match was possible, and 5% (*n* = 16) of symptoms had no reference in the SmPC. A few examples of ADRs without reference in the SmPC were paraesthesia due to exemestane, polyneuropathy due to oxycodone, and urine retention due to midazolam. Table S5 provides the full list of ADRs with no reference in the SmPC.

A total 39 of reADRs were identified, representing over 10% of the identified ADRs; distributed over 17 patients. Twelve of the 39 ADRs reADRs were potentially serious, seven of which were associated with chemotherapy. One reADR resulted in an acute hypersensitivity reaction due to represcription during hospitalization.

STAGE II - COMPARISON OF RULE-BASED AND MANUAL EHR REVIEWS

The rule identified 556 potential ADRs; 179 unique identifications matched the ADRs obtained from the manual EHR review, and 377 potential ADRs were identified as FPs. Of the 318 ADRs identified in the manual EHR review, 179 were also identified by the rule-based review, resulting in a sensitivity of 57% and a PPV of 32%. However, the rule identified eight additional ADRs with a Naranjo score ≥ 1, of which one ADR was classified as serious. Figure 3 presents a Venn diagram of the EHR review methods and the overlap therein.

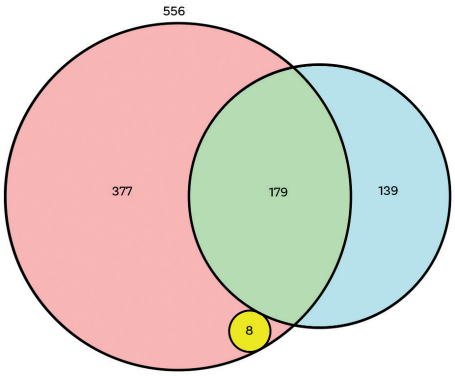


FIGURE 3. *Venn diagram presenting the unique Adverse drug reactions (ADRs).*

The blue circle (n = 318), including the green portion, represents the total number of unique ADRs identified by the manual electronic health record (EHR) review. The red circle (n = 556), including the green and yellow portion, represents the total number of unique ADRs identified by the rule-based EHR review (true positives + false positives). Red circle component (n = 377) represents the false positives. The green section (n = 179) represents the number of true positives. The yellow circle represents the ADRs found only by the rule-based EHR review.

TABLE 3. *True positives and false positives per search strategy identifying ADRs.*

Nr.	Search strategies	Included trigger words		TPs		FPs		PPV
				n	**%**	**n**	**%**	**%**
S1	Keywords implying an ADR	conjugations of	drug-induced	20	10	5	1	80
			allergy	17	8	80	21	18
			side-effect	21	10	10	3	68
			intolerance	0	0	0	0	n/a
			reaction	1	0	2	1	33
			toxicity	13	6	1	0	93
S1 Total / overall ADRs found by keywords				*72*	*35*	*98*	*26*	*42*
S2a	Prepositions followed closely* by a drug group*, a generic drug name, a drug brand, trade name or abbreviation a drug, or drug therapy***	conjugations of	by	16	8	19	5	41
			with	55	27	44	12	56
			after	12	6	67	18	15
			of	31	15	62	16	33
			on	5	2	73	19	6
			since	2	1	12	3	14
S2b	Abbreviations using the included prepositions	conjugations of	as a result **of** / because **of**	0	0	1	0	0
			based **on**	3	1	0	0	100
			as a consequence **of**	4	2	1	0	80
S2 Total / overall ADRs found by a combination of predisposition and drug name				*128*	*62*	*278*	*74*	*31*
S3	Content of forms labeled⁺	conjugations of	allergies:	0	0	0	0	n/a
		conjugations of	anaphylaxis:	0	0	0	0	n/a
S3 Total / overall ADRs found in labeled allergy and anaphylaxis forms				*0*	*0*	*0*	*0*	*n/a*
S4	*Content of complication registration containing key field drug-induced*	-	-	*0*	*0*	*0*	*0*	*n/a*
S5	Content of ADR module	-	-	6	3	0	0	100
S5 Total / overall ADRs found in ADR module				*6*	*3*	*0*	*0*	*100*
Total ADRs identified				*206*	*100*	*377*	*100*	*35*

* The maximum number of characters (i.e., proximity between a preposition and drug name) was set at 16.
** Drug group names were based on the ATC therapeutic subgroup, pharmacological subgroup, chemical subgroup, or chemical substance (i.e., 2nd to 5th levels of ATC main groups classified by WHO).
*** Examples being PPI (proton-pump inhibitor), HCTZ (hydrochlorothiazide), FOLFOX (combination therapy of fluorouracil and oxaliplatin). A full list of abbreviations is provided in Table S2.
⁺ Forms labeled allergy and anaphylaxis using free-text entries were applied prior to the ADR module's introduction in 2015.
PPV = positive predictive value, TPs = true positives, and FPs = false positives

TABLE 4. *Analysis of false negatives.*

Nr.	Search strategies (*n* = 139)		*n*	%
	Missing conjugations of	drug-induced	3	2.2
		allergy	0	0.0
		side-effect	3	2.2
		intolerance	0	0.0
		reaction	0	0.0
		toxicity	0	0.0
S1	***Potential improvement: using keywords implying ADRs***		***6***	***4.4***
	> 16 characters between the preposition and drug name		2	1.4
	Missing synonyms for drug names		44	31.7
	Missing abbreviations		6	4.3
	Missing prepositions		2	1.4
	DD		3	2.2
S2	***Potential improvement:*** using prepositions followed *closely* by a drug group*, a generic drug name, a drug brand, trade name or abbreviation a drug, or drug therapy****		***57***	***41.0***
S3	***Potential improvement:*** *in ADRs found in labeled allergy and anaphylaxis forms*		***0***	0.0
	Specific missing complication fields		3	2.2
S4	***Potential improvement:*** *Content of complication registration containing key field drug-induced*		***3***	***2.2***
S5	***Potential improvement:*** *found in ADR module*		***0***	0.0
	MedDRA + drug name		3	2.2
	Drug name + MedDRA		24	17.3
	Missing synonym of MedDRA term		2	1.4
aS6	***Opportunity for additional strategy:*** *MedDRA term mentioned in text combined with drug name*****		***29***	***20.9***
	Cannot tolerate		2	1.6
aS7	***Opportunity for additional strategy:*** *Abbreviations of cannot tolerate*		***2***	***1.6***
	No obvious additional strategy[+]		***42***	***30.2***

* The maximum number of characters between the preposition and drug was 16.
** Drug group names used were based on the ATC therapeutic subgroup, pharmacological subgroup, chemical subgroup, or chemical substance (i.e., 2nd to 5th levels of ATC main groups classified by WHO)
The maximum number of characters, i.e., proximity, between a preposition and drug name was set at sixteen.
**** MedDRA term and drug name are mentioned within 16 characters of each other
[+] No simple rule-based strategy was thought of to identify these ADRs

STAGE II - ANALYSIS OF RULE-BASED EHR STRATEGIES

Table 5 presents the TPs, FPs, and PPVs for the different search strategies including their stratifications. The total TPs per strategy is higher than the number of unique ADRs that were correctly identified using multiple search strategies. The rule based-model correctly identified 179 unique ADRs. Of these 179 ADRs, 159 were identified using only one strategy, 19 were identified using two strategies (S2 *with* + S1 *drug-induced* *n* = 7; S2 *with* + S2 various *n* = 7; S1 *drug-induced* + S2 *of* *n* = 2; S2 *by* + S2 *of* *n* = 2; ; S1 *drug-induced* + S1 *allergy* *n* = 1), and four were identified using three strategies (S1 *drug-induced* + S1 *toxicity* + S2 *of* *n* = 2; S1 *allergy* + S1 *reaction* + S2 *on* *n* = 1; S2 *by* + S2 *with* + S2b *a.c.o.* *n* = 1), which adds-up to 206 true positive identifications.

Overall the search strategy using prepositions followed by a drug name or group (S2) accounted for 62% (n=125) of the identified ADRs, while using keywords (S1) accounted for 35% (n=72), and only 3% (n=6) were identified using the ADR module (S5). Within S1 the most effective keyword was *toxicity* (PPV of 93%) which identified 6% (*n* = 13) of the ADRs. Less effective, although with a higher yield, were the keywords *drug-induced* (PPV 80%, *n* = 20) and *side-effect* (PPV 68%, *n* = 21). Within S2, the preposition with the highest yield was *with* (46 TPs, PPV 32%). The term *based on* had a PPV of 100%, although it identified only two ADRs. The FPs related to S2 were responsible for 74% of the total ADRs, followed by words forming abbreviations of *allergy* (21%, n = 80). Naranjo causality score and SmPC reference did not markedly increase or decrease the sensitivity of the rule-based review, nor did the system organ class on which the ADR had effect or the type of medication. However, ADR potential seriousness increased the sensitivity to 67% (41/66) compared to 55% (138/252) for non-serious ADRs.

STAGE II – FALSE-NEGATIVES ANALYSIS

Table 4 shows the analysis and categorization of the false negatives (n=139). S2 accounted for most the of the false negatives, 41% (n=57). Within S2, abbreviations of drug names (31.7%, n=44) were the most common cause, missing abbreviations (4.3%, n=6) were the second most common cause. Other search strategies used S1 and S3 respectively accounted for six (4.3%) and three (2.2%) false negatives. Two additional strategies were uncovered from the analysis of the false negatives. The most promising additional strategy (aS6), being usage of MedDRA terms combined with drug names in close proximity to each other (16 characters), which would identify an additional 29 ADRs. The second additional strategy would be adding abbreviations of 'can not tolerate', adding an additional two positively identified ADRs. For 30.2% (n=38) of false negative ADRs, no simple rule-based identification strategies were uncovered. ADRs not mentioned in physician notes were less likely to be identified and were responsible for 44% (54/122) of the FNs.

DISCUSSION

This study describes the first steps in the development of an automated tool for identifying ADRs using free-text in hospital EHRs. To our knowledge, this is the first study describing strategies to identify ADRs from a hospital EHR, using all types of free-text EHR notes and including all types of ADRs. Furthermore, it is the first to consider the causality of the potential ADRs. During stage I, the manual review of ten EHRs, two promising strategies were identified: keywords indicating an ADR and specific prepositions followed closely by medication names. In stage II, 45 complete EHR histories were manually reviewed and compared to strategies built into a rule-based model. Despite the early development stage, the rule-based model achieved a sensitivity of 57% and a PPV of 32%. Analysis of the FNs revealed that S1 as well as S2 could potentially be significantly further improved.

Studies of previous ADRs involving hospitalizations have demonstrated that each patient handover is accompanied by information loss, particularly during handovers from hospitals to primary care [22,42]. This study supports these findings within the same hospital and EHR setting. In 32% of cases, no reference was found in physician notes to ADRs recorded by nurses, pharmacy technicians, pharmacists, or other healthcare professionals. These findings also support the hypothesis that focusing on specific EHR notes only partially identifies previous ADRs. Moreover, only 2% of the ADRs had a structured registration, enabling CDS system alerting. Recurrency of ADRs was common: 17 of the 45 patients studied experienced a reADR, and one patient had three recurrences. One of these reADRs resulted in an acute hypersensitivity reaction due to unintended represcription, during hospitalization. While not formally assessed, at least 10% of the ADRs appeared to have been preventable, with a warning during represcription.

Analysis of the FNs revealed possibilities for fine-tuning discovered strategies, such as extending the library of synonyms and abbreviated medication names. However, the analysis also revealed that additional strategies are needed to achieve the desired sensitivity. An obvious strategy would be to include symptoms and side-effects followed or preceded by medication names. While powerful, this strategy may be prone to falsely identifying disease symptoms as an ADR. Moreover, although an extensive, coded database of ADRs was readily available, many of the ADRs were either misspelled, abbreviated, or described in such a way that they were not readily identified in the MedDRA database. As with the G-standard medication database used in the developed tool, the MedDRA database will require extension to include frequently used synonyms and abbreviations. The FP analysis demonstrated that natural language processing techniques are required to understand the context of trigger words, for example, recognizing when effects are considered positive (e.g., *hypernatremia resolved after starting hydrochlorothiazide*). However, several simple modifications could potentially significantly reduce FPs. The first would be to extend the library of disregarded text strings; this could reduce the number of FPs resulting from the

trigger word *allergy* in particular. Secondly, medicine names or abbreviations thereof must be screened to identify those having additional meanings.

One of the limitations of the study methodology was that the identification strategies were based on EHRs originating from a single hospital, using one EHR system, while language use may differ between hospitals and regions. Furthermore, only EHRs of patients were included recently hospitalized to a ward focusing on internal medicine. The language used by healthcare professionals may vary according to their specialisms. Scanned documents were discarded, thereby potentially missing ADRs, particularly since referral letters often contain ADR information. These limitations may have resulted in a failure to discover key identification strategies and an overestimation of the rule's performance. Nevertheless, the EHR history contained notes from ambulant visits and hospitalizations related to several medical specialisms (n = 12), and the ADRs were recorded by a large number of diverse healthcare professionals (n = 206). The Naranjo algorithm was used to assess causality of the ADRs. There is however much debate on the reliability of this and other algorithms to assess causality, this because of problems with reproducibility and validity. However, 'no method is universally accepted for causality assessment of ADRs'.[43] The Naranjo algorithm was chosen as it is still the preferred method for causality assessment in the Netherlands by pharmacovigilance authorities and healthcare professionals. At least possible (equal or higher than zero) ADRs were included. It could be argued that only a score of equal or higher than five or even equal or higher than nine should be used for inclusion. However, the primary aim of the study was to discover strategies identifying EHR notes possibly containing ADRs, for this purpose it is useful to include all possible ADRs. Excluding type E-F ADRs could be seen as a limitation. Current CDS systems however, would not be able to generate alerts on E and F type ADRs.

The first step to further develop the tool would be to translate the search strategies and logic to programming more suitable for natural language processing (e.g., Python or R). This process would also create the possibility to add fuzzy logic and use artificial intelligence techniques such as machine learning. The developed rule-based model retrieved items of text referring to ADRs. However, it did not extract and code the ADRs and associated medication, which would be required to avoid duplicating identified ADRs and essential before feeding ADRs back to the EHR for use in a CDS system. Therefore, the second step would be to automatically extract and code the ADRs from the identified text strings. Also, for a tool to fully utilize all available free-text in the EHR, optical character recognition software must be considered before processing the text. At the back end of the tool, a CDS system could be used to extract valuable information to contextualize the retrieved ADR. For example, if the tool returns *hypernatremia* due to *diuretic*, the CDS system can retrieve the specific medication and dose used from the CPOE. After such developments, the tool should be tested on a different hospital EHR to study the generalizability and usability of the tool.

Using ADRs registered in free-text as input for CDS system to alert physicians would be a considerable advance to reduce the number unintended represcriptions. It is however important to consider that there is also an overall under-reporting of ADRs by healthcare professionals[44], therefore the implementation of tools to detect ADRs from free-text will never solve the entire problem. Considerable attention should therefore also be given to directly improve ADR registration by patients as well as healthcare professionals. Education and electronic reminders can help to improve the feeling of support from social environment and recognition of the importance of correct ADR registration.[45,46] Also, improving EHR systems in such a way to make it easier and less time consuming to properly register an ADR can markedly improve registration.[47] Introducing patient self-reporting within the EHR patient portal would possibly also increase the number of ADRs registered.[48]

CONCLUSION

Two key strategies were developed to identify ADRs from free-text in a hospital EHR. These strategies show promise, warranting further study and the development of a tool to alert healthcare professionals to previously experienced ADRs.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found at:
https://bpspubs.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fbcp.15068&file=bcp15068-sup-0001-supporting+information.docx

Or by scanning the QR code:

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3

PREVENTION OF POTENTIAL ADVERSE DRUG EVENTS

CHAPTER 3.1

Clinical decision support system-assisted pharmacy intervention reduces feeding tube-related medication errors in hospitalized patients: a focus on medication suitable for feeding tube administration

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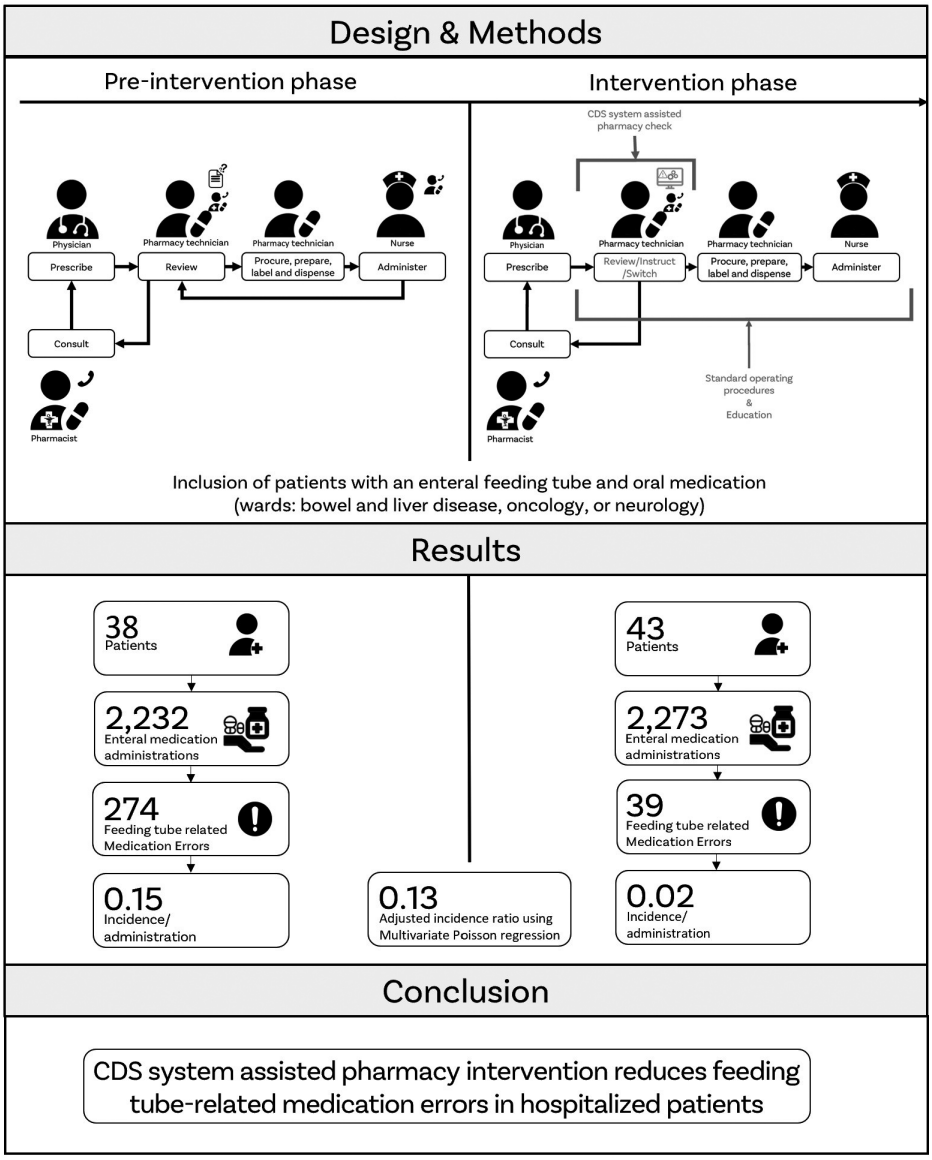
GRAPHICAL ABSTRACT



ABSTRACT

BACKGROUND

Administering medication through an enteral feeding tube is a frequent cause of errors resulting in increased morbidity and cost. Studies on interventions to prevent these errors in hospitalized patients, however, are limited. Objective: To study the effect of a clinical decision support (CDS system) system assisted pharmacy intervention on the incidence of feeding tube-related medication errors (FTRMEs) in hospitalized patients.

METHODS

A pre-post intervention study was conducted between October 2014 and May 2015 in the Catharina Hospital, the Netherlands. Patients admitted to the wards of bowel and liver disease, oncology, or neurology, using oral medication and had an enteral feeding tube were included. Pre-intervention patients were given care as usual. The intervention consisted of implementing a CDS system assisted pharmacy check while also implementing standard operating procedures and educating personnel. An FTRME was defined as the administration of inappropriate medication through an enteral feeding tube. The incidence was expressed as the number of FTRME per medication administration. Multivariate Poisson regression was used to calculate the incidence ratio (IR) comparing both phases.

RESULTS

Eighty-one patients were included, 38 during pre-intervention and 43 during intervention phase. Incidence of FTRMEs in the pre-intervention phase was 0.15 (95% confidence interval (CI) 0.07–0.23) versus 0.02 (CI 0.00–0.04) in the intervention phase, resulting in an adjusted IR of 0.13 (CI 0.10–0.18). Discussion: Incidence of FTRMEs as well as the IR are comparable to previous studies.

CONCLUSION

The intervention resulted in a substantial reduction in the incidence of feeding tube-related medication errors.

INTRODUCTION

A substantial number of hospitalized patients are temporarily dependent on enteral feeding[1] and are unable to swallow medication.[2] Liquid, transdermal, rectal, and even intravenous formulations are frequently unavailable or undesirable. As such, medication is frequently administered through the enteral feeding tube (FT). Previous studies demonstrated that incorrect administration of oral medication through a FT, like crushing formulations which may not be crushed, is a frequent cause of medication errors.[2,3] Medication errors can result in obstruction of the FT[3,4], resulting in increased morbidity[5-7] and cost[8]. Such medication errors can directly harm the patient 9-12 or constitute an health risk for medical personnel[13,14].Various approaches have been studied to reduce the number of feeding tube-related medication errors (FTRMEs). In one study performed in an institution for individuals with intellectual disability (*n* = 6; 245 administrations), introducing a nurse training program reduced the number of FTRMEs significantly by 70%.[15] A comparable study performed in nursing home patients (*n* = 197; 681 administrations) added warning symbols on the unit dose for packaged and labelled medications, significantly reducing the number of FTRMEs by 85%.16 In hospitalized patients (*n* = 16; 183 administrations), adding standard operating procedures and daily ward visits by pharmacy technicians and alerting in the computerized physician order entry (CPOE) decreased the number of FTRMEs even further, by 93%.[2]

Using the Swiss cheese model[17] to analyze the process of medication use in patients with a FT, it is striking to observe that in current practice, the nurse administrating the medication is often the only layer of security to prevent an FTRME, meaning that errors are symptoms of a flawed system. Welie *et al.* and Idzinga *et al.* focused on improving this security layer[15,16], but this still preserves a single point of failure. Van den Bemt *et al.* added two additional layers of security; however, it was at the expense of an increase in staffing, which could provide difficulties in scaling up.[2] Additionally, independently of the chosen approach, nurses and physicians were still responsible for choosing an appropriate alternative while frequently unaware that altering formulation may require a dose adjustment, a change in frequency of administration, or therapeutic drug monitoring.

A new security layer was developed, designed to be scalable and without the need for additional staffing. This extra layer was designated the 'clinical decision support (CDS) system assisted pharmacy check.' The pharmacy check consisted of a pharmacy technician autonomously switching medication to a liquid formulation, changing the route of administration, or outlining the correct administration method in the electronic administration instruction based on a tailored CDS alert, making it suitable for oral as well as enteral administration. Added to this new component were components already known to be effective, including implementation of standard operating procedures and training of staff. The aim of the study was to evaluate the effect of the CDS system assisted pharmacy intervention on the incidence of potential FTRMEs in hospitalized patients.

METHODS

SETTING, STUDY POPULATION, AND DESIGN

This pre-post intervention study was performed on three wards of the Catharina Hospital Eindhoven, a 700-bed teaching hospital in the Netherlands. The three wards were bowel and liver disease with 32 beds, oncology with 28 beds, and neurology with 31 beds. The hospital used CS-EZIS® (version 5.2, Chipsoft BV, Amsterdam) as its electronic health record (EHR) system. All relevant medical data were ordered and stored in this system, including medication and usage of FT. To provide medication-related clinical decision support, including decision support during the study, the hospital used a separate CDS system, being Gaston Pharma® (version 2.8.2.100, Gaston Medical®, Eindhoven). To provide pharmaceutical services for these three wards, three pharmaceutical technicians were available on workdays. Pharmaceutical services included medication review, medication distribution, and medication preparation. There was also one pharmacist on duty dividing their attention amongst all wards.

Pre-intervention inclusion started October 2014 and lasted until December 2014. This was followed by a three-month period of the implementation of the CDS system assisted pharmacy intervention. The intervention focused on improving the medication process for patients with FT and consisted of implementing standard operating procedures, training of personnel, and the CDS system assisted pharmacy check. The intervention is described in more detail in the section on implementing the intervention. Inclusion for the intervention phase started March 2015 and ended May 2015. All patients on the respective wards who had a FT for more than 24 hours and were prescribed oral medication were included. Patients could be included in only one of the phases. Re-hospitalizations of patients during the same phase were cumulated and calculated as a single inclusion. Information on enteral feeding tube status was based on the paper ward lists collected from the respective wards, FT status from the EHR was also collected, but was found to be incomplete. The ward list stated basic patient information such as name, patient number, reason of admission, comorbidities important for nursing, frequency of checking vital signs, mobility of the patient, enteral feeding tube type and amount of feeding, 'Do Not Reanimate' (DNR) code, particularities to medication. Figure S1 shows an example of such a ward list. The total of registered enteral feeding tube days was equal to the sum of days that the enteral feeding tube was mentioned on that ward list. General patient characteristics, tube characteristics, medication orders, and medication administrations were extracted from the EHR. When medication was listed as 'when necessary' or 'pro re nata' (p.r.n.). in the EHR and was not "checked" as being administered or "checked" to be unnecessary by a nurse, it was counted as a medication administration. The study was approved by the local medical ethics committee.

PRE-INTERVENTION PHASE

During the pre-intervention phase, care was provided as usual. The medication process for patients with a FT during this phase is graphically represented in figure 1 on the left side. During the day, the nurse informed the pharmacy technician if a FT was placed. When informed, the pharmacy technician manually checked each medication order, using a local protocol, comparing the medication to a list of crushable medication. When the medication was not on the list of crushable medication, the pharmacy technician contacted the pharmacist. Subsequently, the pharmacist contacted the physician to discuss alternatives. The physician was eventually responsible for changing the medication order. After hours, the nurses themselves were responsible for manually checking each medication order, using the list of crushable medication, before administering medication. If the medication was not on the list, the nurse could consult the pharmacist.

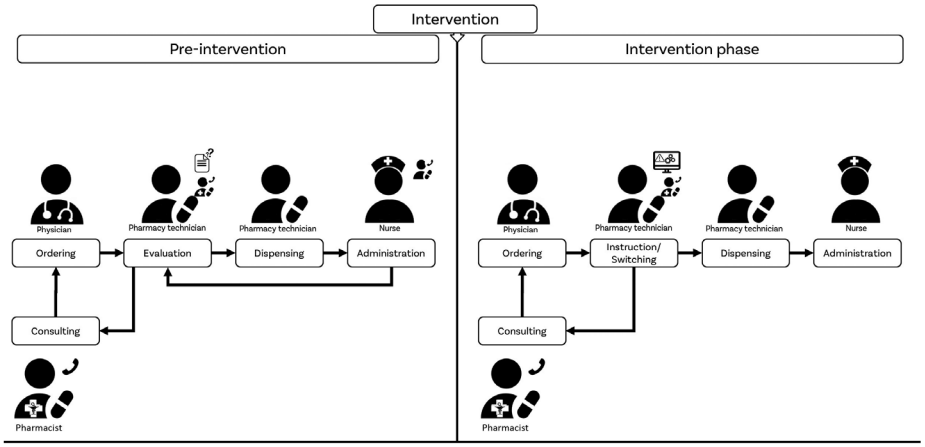


FIGURE 1. *Graphical representation of the daytime medication process in the pre-intervention and intervention phases. The four steps correspond to the EN use process as presented in Boullata et al. and the medication use process.*[18] *On the right side in grey the components of the intervention. The icon of a document represents a manual check of medication using local protocol. The icon of a monitor with an alert icon and turning gears represents the CDS system with specific alerts. The telephone icon represents a telephonic consultation.*

IMPLEMENTATION OF THE INTERVENTION

The intervention comprised implementing standard operating procedures on medication administration through a FT, training of pharmacy technicians and nurses on the subject, and implementing a CDS system assisted pharmacy check. The standard operating procedures and training were based on ASPEN recommendations and results from previous studies[2,15,16,18]. The input and recommendations for the CDS system were based on local guidelines and the Dutch Oralia VTGM database[19]. The recommendation on medication formulation was, if relevant to the recommendation, tailored to type, material and position

of distal tip of enteral feeding tube. Additionally, an expert team evaluated the medication orders of the included patients in the pre-intervention phase to identify common FTRMEs and formulate specific recommendations. These were used to improve the CDS system content and alerts. Details on the expert team are provided further on.

INTERVENTION PHASE

The process during the intervention phase is graphically represented at the right side of figure 1. The CDS system assisted pharmacy check consisted of the CDS system generating tailored alerts for each patient and the pharmacy technician evaluating these alerts and acting accordingly. The CDS system generated alerts if one of two following conditions were met: (1) an enteral feeding tube was electronically ordered in the previous 24 hours and non-crushable medication was used or if the medication used was not part of the CDS system database, (2) when inappropriate medication was ordered in the previous 24 hours for a patient with a enteral feeding tube. The CDS system alert text started with information on type, position of distal tip and date and time of placement of the FT. This was followed by a table with tailored recommendations for the most encountered incorrectly prescribed medication. Moreover, the alert consisted of a list of medications with no specific recommendation, so the pharmacy technician had to check these medication orders manually making use of the Oralia VTGM database.[19] An example of a CDS system alert is shown in figure S2. Alerts were generated once daily between 06:00 and 06:30. Between 09:00 and 13:00 of the same day, the alerts were evaluated by the pharmacy technicians. The pharmacy technicians autonomously adjusted medication orders according to the alerts generated by the CDS system. All adjustments were double checked by another pharmacy technician and later by a pharmacist. If the medication order other than formulation and/or frequency of administration needed to be adjusted, the pharmacy technician contacted the pharmacist. The pharmacist called the physician and advised on alternatives and/or necessary therapeutic drug monitoring.

PRIMARY OUTCOME MEASURE

The primary outcome measure of the study was the number of FTRMEs per medication administration.

FEEDING TUBE-RELATED MEDICATION ERRORS

An FTRME was defined as the administration of unsuitable medication through a FT. Unsuitable being all medication formulations, according to Dutch Oralia VTGM database, which cannot be safely administered through a FT with or without modification of medication formulation, taking into account FT diameter, FT material and position of distal tip. Medication prescribed orally, given enterally was not considered a FTRME as the CPOE does not provide a possibility to choose enteral administration route. The FTRMEs were

categorized in three groups: errors leading to increased toxicity or decreased effectivity, errors leading to increased risk to medical personnel, or errors leading to increased risk of tube obstruction. Medication with an enteric-coated formulation, a modified-release formulation, or a liquid-filled hard capsule formulation were categorized as errors leading to increased toxicity or decreased effectivity. Hazardous medication that led to increased risk for medical personnel were subcategorized into one of four categories: immunosuppressing, cytotoxic, sensitizing, and a residual category for otherwise harmful medicine. Medication described or known to increase risk of FT obstruction, not falling in the previous categories was classified as: errors leading to increased risk of tube obstruction.

In addition to groups based on risk, FTRMEs were also classified as being easily preventable or hard to prevent. Easily preventable errors were FTRMEs that had one of the following alternatives: liquid or dispersible formulation suitable for enteral administration, normal release formulations without coating known to be suitable for enteral administration, alternate route of administration (rectal or transdermal), or an available therapeutic alternative. Medication lists for all included patients were evaluated by an expert team to determine to presence and category of an FTRME based on the aforementioned criteria, no observations of medication preparation or enteral administration were performed as part of the study. The expert team consisted of two senior hospital pharmacists, a nurse specializing in enteral tube feeding and a dietician specializing in enteral nutrition. Evaluation of the medication lists was done independently by each expert. Differences in evaluation were discussed in a plenary meeting were consensus was required to mark an administration as FTRME.

DATA ANALYSIS

Patient characteristics were compared using the χ^2 test for differences in proportions, a t-test for differences in means, and a Mann–Whitney U test to compare medians. The incidence was calculated as the number of FTRMEs per medication administration. A multivariate Poisson regression was used to compare the incidence ratios (IRs) of the FTRMEs between both phases. Poisson distribution assumes that the number of events has a fixed time interval, occur at random, occur independently in time, and occur at a constant rate. Because these assumptions were not necessarily true for this study, the number of administrations, the number of days at risk, feeding tube days, and the number of unique drugs were tested as covariates to compensate for possible distortions in Poisson distribution. Forward selection was used to include variables in the multivariate model. If a covariate had $p < 0.05$ in the forward selection and final model, it was included in the multivariate analysis. Statistical analyses were performed using SPSS (IBM SPSS® statistics version 25).

RESULTS

Eighty-one patients were included in the study, 38 during pre-intervention and 43 in the intervention phase. Overall, of the included patients, 25 were admitted to the bowel and liver disease ward, 29 to the oncology ward, and 27 to the neurology ward. Table 1 shows the patient characteristics. There were no significant differences in any of the patient characteristics between the two phases. Patients included into the study had a mean age of 67.5 years. They were hospitalized for a median of 13 days (interquartile range (IQR) 15 days) and used a mean of 10.8 unique medications (standard deviation (SD) 5.8) with a median of 36.5 oral medication administrations (IQR 70). It is worth mentioning that the ward list did not specify were the enteral feeding tube ended in the gastro-intestinal (GI) tract in more than 50% of the patients.

TABLE 1. *Comparison of patient characteristics before and after intervention.*

Variable	Pre-intervention *n* = 38		Intervention *n* = 43		*p*-value
Mean age in years (SD)	68.7	(13.8)	66.4	(15.0)	0.47[b]
Median hospitalization in days (IQR)	15	(12)	12	(18)	0.87[c]
Gender (%)					
Male	26	(68.4)	26	(60.5)	0.56[a]
Female	12	(31.6)	17	(39.6)	
Ward (%)					
Bowel and liver disease	11	(28.9)	14	(32.6)	0.81[a]
Oncology	15	(39.5)	14	(32.6)	
Neurology	12	(31.6)	15	(34.9)	
Medication					
Mean number of unique oral medication used (SD)	11.1	(5.7)	10.6	(5.9)	0.70[b]
Median number of oral medication administrations per patient (IQR)*	36.5	(56)	31	(74)	0.63[C]
Enteral feeding tube					
Median number of enteral feeding tube days (IQR)	4	(5)	4	(6)	0.71[c]
*Type of enteral feeding tube, n** (%)*					
Nasogastric	8	(21.1)	6	(14.0)	0.26[a]
Nasoduodenal	5	(13.2)	2	(4.7)	
PEG gastric/duodenal	2	(5.3)	4	(9.3)	
PEG-J	3	(7.9)	5	(11.6)	
Triple lumen***	0	(0.0)	4	(9.3)	
Unspecified	20	(52.6)	22	(51.2)	

Patient characteristics are shown for unique patients, hospitalized to the ward of bowel and liver diseases, oncology, or neurology in the period 27-10-2014 to 15-05-2015 with a least one day of enteral tube feeding as registered by the nursing staff on the ward list.
[a] Chi-square test; [b] Unpaired two-sample t-test; [c] Mann-Whitney U-test
SD, standard deviation; M, median; IQR, interquartile range.
* Median number of oral medication administrations per patient included after hours administrations
**As stated on ward list
*** Three lumen dual-purpose air-vented assisted gastric aspiration and post-ligament of Treitz enteral feeding tube[20]

In the pre-intervention phase, there were 274 FTRMEs in 209 person days with 2,232 administrations, IR was 0.153 FTMREs per administration (95% confidence interval (CI) 0.07–0.23). In the intervention phase, there were 39 FTRMEs in 233 person days with 2,273 administrations, IR 0.02 FTMRE per administration (CI 0.00–0.04). Univariate comparison of both IRs shows a significant difference in the number of FTRMEs. At least one FTRME occurred in 66% of the included patients pre-intervention compared to 12% in the intervention phase. Of the 39 FTRMEs in the intervention phase, 37 were due to human error by the pharmacy technician overlooking a part of the CDS system recommendation. The remaining two FTRMEs were due a technical error in which the CDS system did not generate a new alert when a patient with an enteral feeding tube in situ was transferred from a ward not participating in the study to one of the study wards.

Table 2 shows the results from the multivariate Poisson regression comparing the incidence ratios. There was a clear and significant reduction comparing the two phases, the incidence ratio (IR) being 0.128 (0.092–0.179), using pre-intervention phase as reference group, $p < 0.001$. The three covariates identified to contribute to the model are also shown in table 2. It is interesting to observe that the number of administrations and number of unique medications used were independently associated with the risk of a FTRME. Univariate Poisson analysis and single covariates are shown in table S1.

TABLE 2. *Multivariate Poisson regression comparing FTRMEs in the intervention phase to pre-intervention.*

Variable	IRR* EXP(B)	95% CI (lower–upper)	*p*-value
Number of feeding tube-related medication errors	0.143	(0.102–0.200)	<0.001
Covariates			
Number of administrations	1.006	(1.005–1.008)	<0.001
Number of unique medications used	1.076	(1.051–1.101)	<0.001
Ward	1.865	(1.583–2.198)	<0.001

Multivariate Poisson regression is shown comparing feeding tube-related medication errors in the intervention phase compared to the pre-intervention, which is the reference population. The bottom part shows all included covariates including their part in the calculated incidence ratio. Covariates were included into the analysis having a $p < 0.05$ when separately tested and $p < 0.05$ when tested in a single model.

* Pre-intervention being the reference population
IR: incidence ratio; 95% CI: 95% confidence interval; Exp: expected count
FTRME: feeding tube-related medication errors

Table 3 shows the distribution of the different types of feeding tube-related medication errors. Most errors, 70% pre-intervention and 90% during the intervention phase, were those that led directly to increased toxicity or decreased effectivity. Within this group, the most common types of errors were crushing medication with an enteric coating, 32% pre-intervention and 8% during intervention phase, and crushing medication with a modified-release formulation, at 31% percent pre-intervention and 69% during the intervention phase. Errors leading to increased risk to medical personnel were the cause of FTRMEs comprised 18% of pre-intervention errors and were nonexistent during the intervention phase.

TABLE 3. *Type of feeding tube-related medication errors.*

Distribution in categories of FTRMEs	**Pre-intervention (patients = 38)**		**Post-intervention (patients = 43)**	
	n	%	n	%
Total FTRMEs	274	(100)	39	(100)
Errors leading to increased toxicity or decreased effectivity	**191**	**(70)**	**35**	**(90)**
Enteric-coated formulation	88	(32)	8	(21)
Modified-release formulation	83[b]	(31)[b]	27[a]	(69)[a]
Liquid-filled hard capsule formulation[+]	20	(7)	0	(0)
Errors leading to increased risk for medical personnel	**49**	**(18)**	**0**	**(0)**
Oral chemotherapy	12	(4)	0	(0)
Immunosuppressants	0	(0)	0[a]	(0)[a]
Sensitizing medication	35	(13)	0	(0)
Other	2[b]	(1)[b]	0	(0)
Errors leading to increased risk of tube obstruction	**34**	**(12)**	**4**	**(10)**

The table shows the different categories of feeding tube-related medication errors for both phases.
Major categories are shown as rows with grey filling and bold font and together sum to 100%. Subcategories are shown in white rows and together count up to the major categories.
[+] Liquid-filled hard capsule formulation not suitable for administration through an enteral feeding tube, not falling apart in water, and having considerable loss when sucked up with a needle.
[a] There were six administrations of immunosuppressant, modified-release tacrolimus, which were included into the category errors leading to increase toxicity or decreased effectivity and subcategory modified-release instead of errors leading to increased risk for medical personnel and subcategory immunosuppressants.
[b] There was one administration of dutasteride/tamsulosin modified-release that was included into the category errors leading to increase toxicity or decreased effectivity and subcategory modified-release instead of errors leading to increased risk for medical personnel and subcategory other.
FTRME: feeding tube-related medication errors

During the pre-intervention phase, 91% of the of the FTRMEs were easily preventable; during the intervention phase it was 90%. Forty-two percent (42%) of the FTRME were preventable because of the availability of a liquid or dispersible alternative; during the intervention phase, this was 76%. In 32% of the cases pre-intervention, choosing a therapeutic alternative, such as switching pantoprazol to esomeprazole, would have prevented an FTRME; during intervention, this was 20%. Another 14% was preventable by switching modified-release preparations to regular tablets given more frequently. In 3% of the cases, a transdermal alternative was available.

DISCUSSION

PRINCIPAL FINDINGS

This study demonstrated that a CDS system assisted pharmacy intervention resulted in an 87.2% reduction of FTRMEs in hospitalized patients. This FTRME reduction was achieved without additional staffing and is thought to be sustainable because of the additional layer of security provided by active alerting using an automated system. The pre-intervention incidence in the study was 1.34 FTMREs/person day showing that nurses are insufficiently aware that much medication may not be crushed whilst in over 90% of the cases alternatives were readily available. Seventy percent of the errors had the potential to directly harm the patient because of increased toxicity; crushing of short-acting beta-blockers, short-acting calcium antagonists, nitrates, opioids, and anti-epileptics; or loss of effectivity.

IMPLICATIONS

The results from this study combined with previous research indicates the necessity for each hospital to have a program to reduce the number of feeding tube-related medication errors. Computerized support could provide an answer for staffing issues as well as relieve pressure on nurses to find correct ways of administering medicine through an enteral feeding tube.

COMPARISON TO OTHER STUDIES

The baseline IR of 0.15 FTRMEs per medication administration is comparable to previous studies, 0.26 in hospitalized patients and 0.04 in nursing home patients[2,16]. The reduction of 87.2% in FTRME is also in line with previous studies having reported reductions of 70%[15], 85%[16], and 93%[2]. Although a comparable IR and reduction were found, it is important to consider that these results were purely based on a reduction of unsuitable medication choice and did not take into account administration errors such as not flushing the enteral feeding tube before and after administration, thus making it likely that there was an underestimation of true FTRME incidence in this study. Van den Bemt *et al.* added two additional layers of security; however, it was at the expense of an increase in staffing, which could provide difficulties in scaling up.[2]

LIMITATIONS

One of the limitations of the study is the chosen design. An RCT design or a time series analysis would have ruled out bias due to different patient characteristics and time trends. However, no differences were identified in respect to patient characteristics, making selection bias unlikely. Moreover, pre-intervention and intervention period were in short succession, making a time trend also unlikely. Additionally, the measured effect was very substantial and in line with the effect measured in previous studies[2,3,15,16]. In over half the patients, FT entry

point, position of distal tip and diameter of the FT was not recorded on the ward list or in the EHR. While this made FTRME estimation more difficult, if an administration was judged to be an FTRME the chosen medication formulation was unsuitable for types and endings of FT. In contradiction to ASPEN recommendations, all medication was prescribed orally and physician was not alerted during prescribing that medication might be administered through a FT. Another limitation of the study was that it was performed in a single center with a specific CDS system, which may restrict the generalizability of the results. Current intervention also did not change the enteral use process starting after hours.

CURRENT PRACTICE AND FUTURE CONSIDERATIONS

Despite the sizable reduction in FTRMEs, 37 errors were made during the intervention phase. All of these were attributable to human error, such as a pharmacy technician overlooking a suggested substitution and the nurse not being alarmed by crushing a modified-release or enteric-coated formulation. To overcome these errors, a second evaluation of all alerts by a second pharmacy technician has become part of the standard operating procedures. Since study ending the CDS system assisted pharmacy intervention has become part of routine care for all wards, seven days a week. To aid nurses after hours, a nurse and mobile friendly version of the Dutch Oralia VTGM database has been made available. During the study, in over half the patients FT registration in the EHR and on the ward list lacked important aspects of the FT. Knowing all aspects of the FT however is crucial to safely choose, prepare and administer medication enterally. Moreover, it is also vital to generate the correct CDS system recommendations. Therefore, additional attention should be given during training to record all FT aspects correctly. Analysis of alerts and comments revealed that further improvements to the FT clinical rule were possible, such as extending the number of specific recommendations, which would reduce the time needed to handle the alerts.

CONCLUSION

The incidence of feeding tube-related medication errors can be substantially reduced by a CDS system assisted pharmacy intervention, consisting of implementation of standard operating procedures, training of personnel, and a CDS system assisted pharmacy check.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found at:
https://aspenjournals.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fjpen.1869&file=jpen1869-sup-0001-SuppMat.docx

Or by scanning the QR code:

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CHAPTER 3.2

Clinical rule-guided pharmacists' intervention in hospitalized patients with hypokalemia: a time series analysis

Link to publication:

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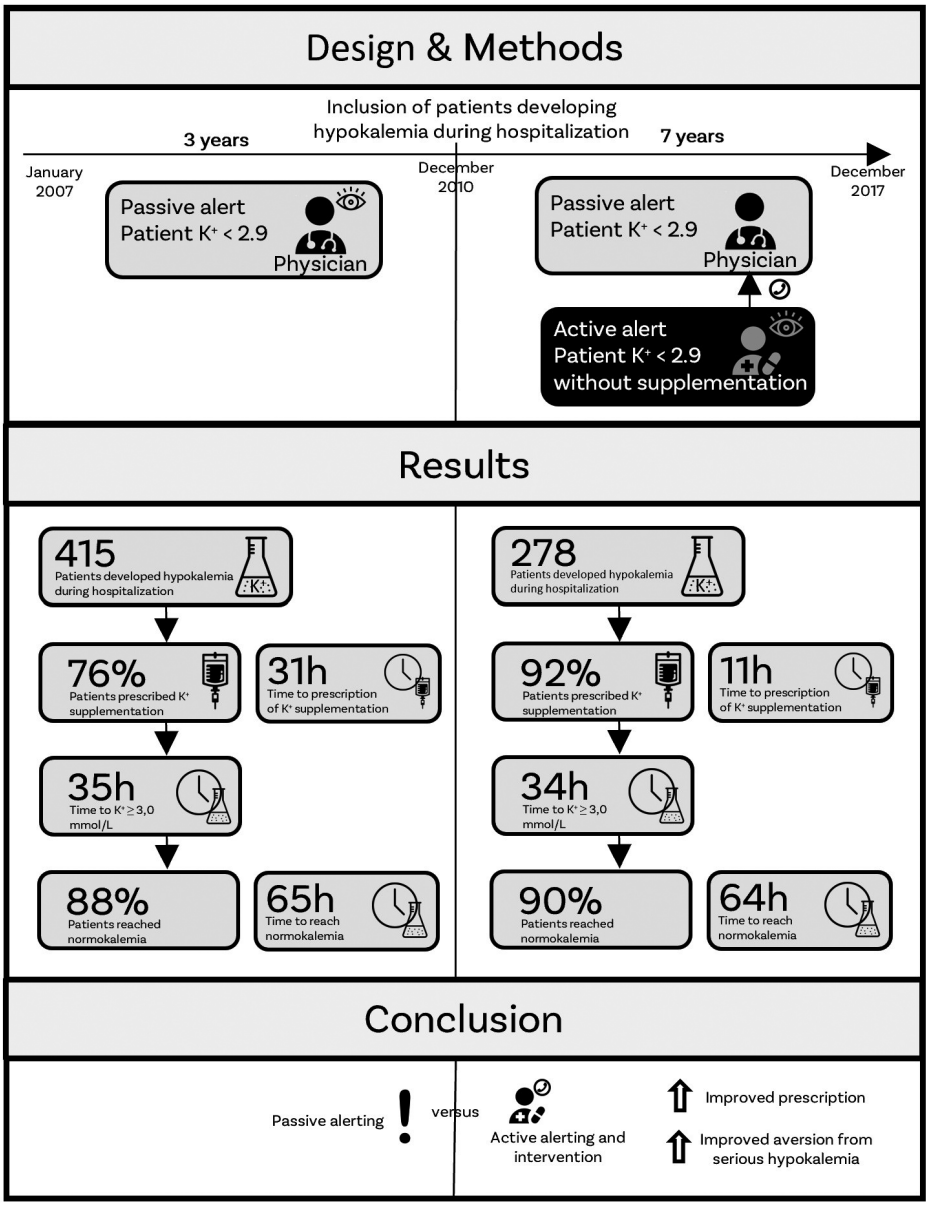
GRAPHICAL ABSTRACT



ABSTRACT

WHAT IS KNOWN AND OBJECTIVE

Physicians' response to moderate and severe hypokalemia in hospitalized patients is frequently suboptimal, leading to increased risk of cardiac arrhythmias and sudden death. While actively alerting physicians on all critical care values using telephone or electronic pop-ups can improve response, it can also lead to alert fatigue and frustration due to nonspecific and overdue alerts. Therefore, a new method was tested. A clinical rule built into a clinical decision support (CDS) system generated alerts for patients with a serum potassium level (SPL) <2.9 mmol/L without a prescription for potassium supplementation. If the alert was deemed clinically relevant, a pharmacist contacted the physician. The aim of this study was to evaluate the impact of the clinical rule-guided pharmacists' intervention compared to showing passive alerts in the electronic health records on outcome in patients who developed hypokalemia (<2.9 mmol/L) during hospitalization.

METHODS

A before (2007-2009) and after (2010-2017) study with time series design was performed. Pre-intervention, physicians were shown passive alerts for hypokalemia in the electronic health records. During the intervention period, in addition to these passive alerts, a pharmacist provided the physician with a specific advice on patients with untreated hypokalemia, guided by the generated alerts. Unique patients >18 years with SPL <2.9 mmol/L measured at least 24 h after hospitalization in whom no potassium supplementation was initiated within 4 h after measurement and normalization of SPL was not achieved within these 4 h, were included. Hemodialysis patients were excluded. The percentage of hypokalemic patients with a subsequent prescription for potassium supplementation, time to subsequent potassium supplementation prescription, the percentage of patients who achieved normokalemia (SPL ≥3.0 mmol/L), time to achieve normokalemia, and total duration of hospitalization were compared.

RESULTS AND DISCUSSION

Six hundred ninety-three patients were included, of whom 278 participated in the intervention phase. The percentage of patients prescribed supplementation as well as time to prescription improved from 76.0% in 31.1 h to 92.0% in 11.3 h (p <0.01). Time to achieve SPL ≥3.0 mmol/L improved, p <0.009. No changes, however, were observed in percentage of patients who achieved normokalemia or time to reach normokalemia, 87.5% in 65.2 h pre-intervention compared to 90.2%, (p =0.69) in 64.0 h (p =0.71) in the intervention group. A non-significant decrease of 8.2 days was observed in duration of hospitalization: 25.4 compared to 17.2 days (p =0.29).

WHAT IS NEW AND CONCLUSION

Combining CDS system alerting with a pharmacist evaluation is an effective method to improve response rate, time to supplementation, and time to initial improvement, defined as SPL ≥3.0 mmol/L. However, it showed no significant effect on percentage of patients achieving normokalemia, time to normokalemia, or hospitalization. The discrepancy between rapid supplementation and improvement on the one hand and failure to improve time to normokalemia on the other warrants further study.

BACKGROUND AND SIGNIFICANCE

Hypokalemia is one of the most frequently occurring electrolyte disturbances in hospitalized patients, with a reported prevalence as high as 20%.[1-4] In contrast to milder hypokalemias (3.4-2.9 mmol/L) which do not always require immediate treatment, hypokalemias below 2.9 mmol/L are independently associated with an increased mortality[5], requiring immediate action, especially in patients with pre-existing cardiac disease.[6-13] Initial corrective action is simple, consisting of potassium supplementation. Thereafter, treatment of underlying causes is indicated, including cessation of drugs contributing to the hypokalemia.[4,7,14,15]

Several studies have shown suboptimal response to moderate and severe hypokalemia in hospitalized patients.[1,10,16,17] A retrospective study performed in a population of 866 hospitalized patients with hypokalemia <3.0 mmol/L reported that in 24% of the patients, no potassium supplementation was administered. Moreover, in 33% of these cases, no follow-up testing of serum potassium level (SPL) was performed. Failure to initiate appropriate treatment led to failure in achieving normokalemia, prolonged hospital stay, and increased in-hospital mortality.[17] A retrospective study that investigated prevalence and symptoms of hypokalemia in emergency department patients found that 45% of the 54 patients with SPL <2.5 mmol/L received no treatment during their stay in the emergency department.[1]

Several approaches have been studied to improve physicians' response to critical laboratory values such as severe hypokalemia, including alerting physicians to critical laboratory values by phone[18,19], by SMS[20,21], and by computerized reminders or pop-ups within the electronic health record (EHR).[22-24] Such interventions have been shown to improve physicians' response time to prescribe potassium supplementation[18,19,24], increase the percentage of patients on whom follow-up SPL measurement was performed[17], decrease time to mild hypokalemia or normal potassium status[22], increase percentage of patients reaching normokalemia during hospitalization[17], and even decrease the duration of hospitalization.[22]

While computerized active alerting of physicians on all critical laboratory results of hospitalized patients has been shown to be effective in improving physicians response, there is also a downside to solely using automated alerts. Most alerts do not provide tailored advice, and can frequently lead to inadequate follow-up action.[17,25] One study even found a delay in time to normalization of critical care results.[23] Also, the increasing number of active alerts causes alert fatigue and frustration.[20,26,27] Additionally, most studies showing a positive effect of active alerting using automated reminders on patient outcome were conducted before the introduction of fully operational and widely accessible EHRs[17,18,22], making these results difficult to extrapolate to current practice. An EHR integrating real-time laboratory results enables physicians to easily and quickly access all results. Using a basic laboratory-assisting clinical decision support (CDS) system allows for passive alerting on critical laboratory results by highlighting them or placing them on a physicians' worklist,

potentially increasing response rate and time without an active alerting method. Since 2008, this was also the case in the Catharina Hospital. Introduction of the fully operational EHR however also led to an increased automated alerting and frustration to calls on critical care values that have already been acted upon. For that reason at the end of 2008, the medical board decided to cancel all forms of active automated alerts or telephonic consultations for critical care values of hospitalized patients. This decision, however, led to a significant delay in response time to critical care results for individual patients. Therefore, a new combination of CDS system and human evaluation was implemented. An EHR-based clinical rule alert was evaluated on clinical relevance by a pharmacist. If the alert was deemed relevant, the pharmacist consulted the physician with specific advice. To test this approach, a series of clinical rules were designed and implemented to monitor response to critical care values. Hypokalemia was among the first in the series to be implemented and was chosen to be studied in further detail because reaction time and clinical impact could be measured directly. The aim of this study was to evaluate the effect of a clinical rule-guided pharmacists' intervention compared to passive alerts shown in the EHR on patient and process outcomes in hospitalized patients with untreated hypokalemia <2.9 mmol/L.

METHODS

SETTING AND STUDY POPULATION

This before and after study with a time series design was performed in the Catharina Hospital Eindhoven (CZE), a 700-bed teaching hospital in the Netherlands. Patients over 18 years of age who met the following criteria were included: hospitalized during the period of January 2007 to December 2016, having a reported SPL <2.9 mmol/L measured at least 24 h after hospital admittance, no potassium supplementation initiated within 4 h after sampling, and normalization of SPL not established within 4 h. Patients, as well as instances of hypokalemia <2.9 mmol/L, were included only once. Hemodialysis patients were excluded. The hospital used CS-EZIS® (Chipsoft BV, Amsterdam) as its EHR and pharmacy information system; CS-EZIS® also provided basic decision support. Critically low laboratory values, including a SPL <2.9 mmol/L, were marked with a "–" in bold red font next to the result. Online Appendix A shows an example of a critically low laboratory value displayed in the EHR. No other method to report critical laboratory values of hospitalized patients was operational. To generate the clinical rule-based alerts, the CDS system Gaston® (Gaston Medical BV, Eindhoven) was used. The CDS system was purchased in 2006 to develop and study a wide range of advanced decision support interventions including, but not limited to medication related interventions. Other clinical rules were already in use by the clinical pharmacy before implementing the hypokalemia rule, including renal function, opioid-laxative, and gastric protection. No additional training, standard operating procedures, or staffing were required

to implement the intervention, also there was no additional reimbursement to provide additional duties. Staff consisted of six to eight clinical pharmacists and three clinical pharmacists in training. Each day there was one pharmacist on clinical duty responsible for checking medication orders, decision support alerts and telephonic consultations for all hospitalized patients. Approval by the Institutional Review Board was not required for this retrospective study.

DESIGN

The pre-intervention phase ran from January 2007 to December 2009, and the intervention phase ran from January 2010 to December 2016. Figure 1 shows a schematic representation of the study phases. During the pre-intervention phase, only passive alerts were shown in the laboratory section of the EHR. During the intervention phase, the hypokalemia clinical rule generated active alerts, shown to a pharmacist, on all hospitalized patients with hypokalemia <2.9 mmol/L in whom no potassium supplementation had been started in any form.

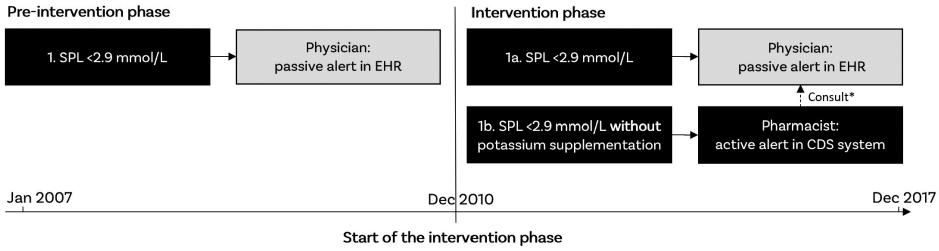


FIGURE 1. *Schematic representation of the chronology of the study design including the alerts generated in both phases of the study.*

SPL: serum potassium level, CDS: computerized decision support, EHR: electronic health record

**Alerts were reviewed by a pharmacist. If an alert was found to be potentially clinically relevant, the pharmacist consulted the physician and provided him or her with treatment advice.*

Figure 1 provides a graphical representation of the clinical rule flow. The alerts generated by the CDS system contained information on: time and result of last SPL, any drugs in use that might contribute to hypokalemia, advice to start oral or intravenous potassium supplementation depending on severity and symptoms, and advice to stop or decrease the dose of the potassium-lowering drugs if applicable. Online appendix C provides a screenshot of an alert provided by the clinical rule in the CDS system module. Alerts were generated once daily between 12:30 and 13:00. Between 13:00 and 17:00 on the same day, all of these alerts were reviewed for clinical relevance by a pharmacist. This review consisted of checking whether potassium supplementation had been prescribed in the meantime, whether SPL had improved in the meantime, additional SPL measurement was ordered in

the meantime and if treatment had been withdrawn in an end-of-life care situation. The advice given by the pharmacist consisted of one or more of the following: advice to start oral or intravenous potassium supplementation, advice to stop or decrease the dose of the potassium-lowering drugs, start or increase dose of potassium sparing diuretic, performing additional SPL measurement, performing an electrocardiogram (EKG) or switching IV fluid suppletion. A recommendation on potassium supplementation dose was only given on request.

ENDPOINTS

The following endpoints included in earlier studies[17-19,22,24] were included as endpoints in the current study: percentage of patients for whom treatment was started[22], time until treatment start[18,19,24], percentage of patients achieving normokalemia[17,18,22], time until normokalemia[18], and duration of hospitalization[22]. Percentage of patients achieving mild hypokalemia, defined as SPL ≥ 3.0 mmol/L, and time to achieve it were added as additional endpoints. These endpoints were added because they most directly reflect response to the intervention. In addition, supplementation of patients with an SPL ≥ 3.0 mmol/L is not directly associated with improved clinical outcomes. Response rate is calculated as the percentage of patients achieving a certain endpoint, and response time as the time until that endpoint is achieved. Taken together, these led to the following four primary endpoints, which were compared to assess the effect of the intervention:

1. prescription for potassium supplementation (a. percentage of patients and b. time to prescription);
2. mild hypokalemia, SPL ≥3.0 mmol/L (a. percentage of patients and b. time to achieve it);
3. normokalemia, SPL ≥3.5 mmol/L (a. percentage of patients and b. time to achieve it);
4. duration of hospitalization.

DATA ANALYSIS

To compare endpoints, a time series analysis was performed using segmented regression with inverse variance-weighted ratios per 12-month period.[28,29] Only the first occurring instance of SPL <2.9 mmol/L was used for each patient. Regressions of the pre-intervention and intervention phases were also compared to the inverse variance-weighted ratios per 12-month period of hospitalization duration of a control population consisting of patients admitted to the hospital in the same period without hypokalemia <2.9 mmol/L. Additional analysis was done to visualize the number datapoints throughout the study. A Durbin–Watson test was performed to check for first-order auto-correlation on all regressions.[30] If first-order auto-correlation was detected, the Prais–Winsten method was used.[31] Statistical analyses were performed using SPSS for Windows, version 25.0.0 (SPSS, IBM, New York). Acceptance rate of the alerts was calculated dividing the number of potassium

supplementation started after telephonic consultation the same day by the total number of telephonic consultations based on generated alerts.

RESULTS

INCLUSION AND EXCLUSION

During the study period there were 295,945 hospitalizations. Including only hospitalizations of adult patients with a SPL <2.9 mmol/L left 3,622 (1,321 pre-intervention versus 2,301 in the intervention phase) hospitalizations. Of these, 2,398 (924 pre-intervention versus 1,474 in the intervention phase) developed hypokalemia <2.9 mmol/L at least 24 h after hospitalization. Sixty-five (25 pre-intervention versus 40 in the intervention phase) patients were excluded based on hemodialysis. Potassium supplementation was already prescribed at the time of SPL sampling in 672 patients (262 pre-intervention versus 410 in the intervention phase) and within 4 h after sampling in 647 patients (189 pre-intervention versus 458 in the intervention phase); these patients were excluded as well. Another 55 patients (20 pre-intervention versus 35 in the intervention phase) were excluded because normal SPL was measured within 4 h after initial sampling. Finally, including only unique patients left 913 eligible for inclusion: 415 patients from the pre-intervention phase and 278 patients during the intervention phase.

PATIENT CHARACTERISTICS

Table 1 shows the patient characteristics of participants included in the analysis. No differences were found in general patient characteristics between the two phases. Median time until first SPL measurement was significantly shorter in the intervention phase, 1.0 h compared to 3.1 h pre-intervention, p =0.003. Related to this, significantly fewer patients had no SPL measured within the first 24 h of hospitalization, 27.0% pre-intervention versus 16.5% in the intervention phase, p =0.004. There was no statistical difference in drug related hypokalemia, 48.7% pre-intervention and 51.8% in the intervention phase, p =0.42. Loop diuretics accounted for the most instances of drug-related hypokalemia, 34.7% and 39.6% respectively also without a statistical difference between the two groups, p =0.19.

TABLE 1. *Comparison of patient characteristics before and after intervention.*

Variable	Pre-intervention phase (n =415)			Intervention phase (n = 278)			*P* value
Mean age in years (sd)	67.9		(14.3)	69.0		(14.9)	0.20
Gender (%)							
Male	161		(39)	106		(38)	0.86
Female	254		(61)	172		(62)	
Treating specialty (%)							
Cardiology	35		(8.4)	35		(12.6)	0.64[$]
Internal Medicine[++]	122		(29.4)	87		(31.3)	
Surgery[+]	157		(37.8)	71		(25.5)	
Intensive care	11		(2.6)	4		(1.4)	
OBGYNUR[+++]	32		(7.9)	37		(13.3)	
Neurology	31		(7.4)	26		(9.4)	
Pulmonology	24		(5.7)	14		(5.0)	
Psychiatry	3		(0.7)	4		(1.4)	
*Onset of initial hypokalemia (%)**							
At admission**	71		(17.1)	51		(18.3)	**0.004**[$]
During hospitalization	223		(55.9)	181		(65.2)	
Unknown (measurement SPL >24h)	112		(27.0)	46		(16.5)	
Median time to first SPL measurement (h)	3.1	Range 1,037.0	IQR 18.3	0.96	Range 165.4	IQR 18.3	**0.003**
Median of first measured SPL (mmol/L)	3.8	Range 6.1	IQR 0.6	3.8	Range 4.9	IQR 0.7	0.58
Potentially drug-related hypokalemia							
Potentially drug-related (%)	202		(48.7)	144	(51.8)		0.42[$]
One drug	175		(86.6)	126	(87.5)		
Two or more drugs	27		(13.4)	18	(12.5)		
Causative drugs in use at time of event (% of total population)							
Loop diuretic	144		(34.7)	110	(39.6)		0.19
Thiazide diuretic	69		(16.6)	41	(14.7)		0.51
Laxative	13		(3.1)	9	(3.2)		0.94
Polystyrene sulfonate	5		(1.2)	2	(0.7)		0.53
Hazardous drugs (%)							
Digoxin	12		(2.9)	11	(4.0)		0.44

Patient characteristics are shown for unique patients over 18 years of age hospitalized in the period between January 2007 and December 2016 with a serum potassium level (SPL) <2.9 mmol/L more than 24 h after hospitalization, no potassium supplementation at or within 4 h after sampling, and no normalization of SPL within 4 h.

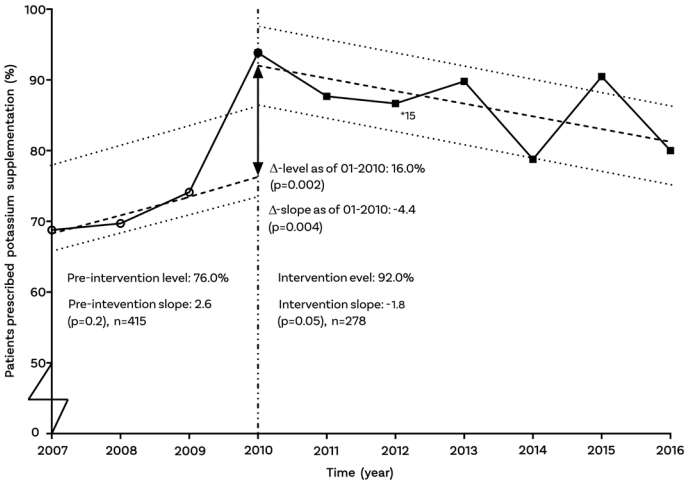
[+] Surgery includes departments of general surgery, cardiothoracic surgery, lung surgery, and orthopedic surgery
[++] Internal medicine includes departments of nephrology, gastrointestinal-and liver diseases, geriatrics, hematology, and oncology
[+++] OBGYNUR includes obstetrics, gynecology, and urology
*patients with a SPL <2.9 mmol/L at admission where not included, therefore at admission SPL was 2.9-3.5 mmol/L
** SPL 2.9-3.5 mmol/L measured within 24 h after hospitalization
[$] Chi-square test was used to test for difference in proportions
sd: standard deviation; IQR: interquartile range; SPL: serum potassium level

ANALYSIS

Figure 2-6 show the time series analyses of the primary endpoints, including intercepts and slopes of all regressions. A significant increase was observed in the percentage of patients subsequently prescribed potassium supplementation, from 76.0% (CI 65.8–86.3%) in the pre-intervention to 92.0% (CI 86.4–97.7%) in the intervention phase, p =0.002. Moreover, time to potassium supplementation was reduced to 11.3 h (CI 5.5–16.9 h) compared to 31.1 h (CI 20.7–41.4 h), p =0.009. The percentage of patients reaching mild hypokalemia, SPL ≥3.0 mmol/L, during hospitalization did not change, 94.1% (CI 84.1–104.2%) pre-intervention compared to 95.8% (CI 90.2–101.3%), p =0.74. No difference between the two was observed in intercepts on time to ≥3.0 mmol/L, 35.2 h (CI 29.1–41.3 h) and 34.2 h (CI 30.8–37.5 h) respectively, p =0.09. However, comparison of slopes shows a significant decrease in time to ≥3.0 mmol/L, from -0.2 (CI -2.9 to -2.5) pre-intervention to -1.7 (CI -2.8 to -0.6) in the intervention phase, p =0.009.

No significant changes were observed in percentage of patients reaching normokalemia or time to reach normokalemia; pre-intervention, 87.5% (CI 72.6–102.3%) reached normokalemia with a mean time intercept of 65.2 h, compared to 90.2% (CI 82.0–98.4%), with a mean time intercept of 64.0 h in the intervention phase, p =0.69 for percentage and p =0.71 for time. A non-significant decrease of 8.2 days was observed in duration of hospitalization, from 25.4 days (CI 11.4–39.2) pre-intervention to 17.2 days (CI 9.5–24.9), p =0.29. No significant change in level or slope was observed for hospitalization in patients without hypokalemia during the same period as the study. Figure 6 shows the number of data points during the entire study period, revealing a trend toward a smaller number of sub-optimally treated incidents of hypokalemia <2.9 mmol/L.

A. Percentage of patients prescribed potassium supplementation



B. Time to prescription of potassium supplementation

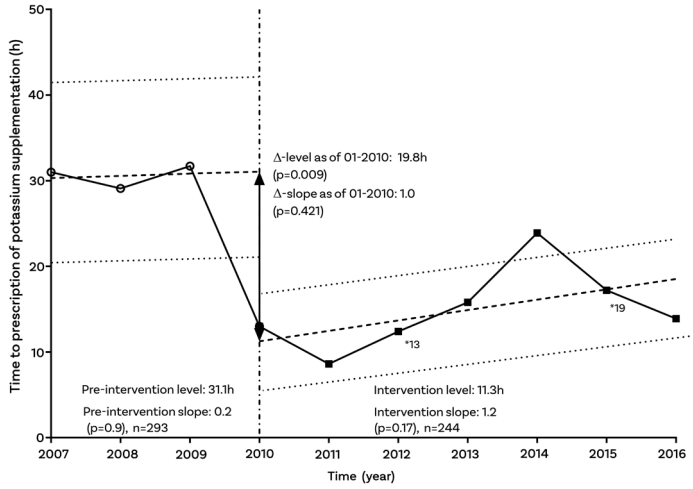
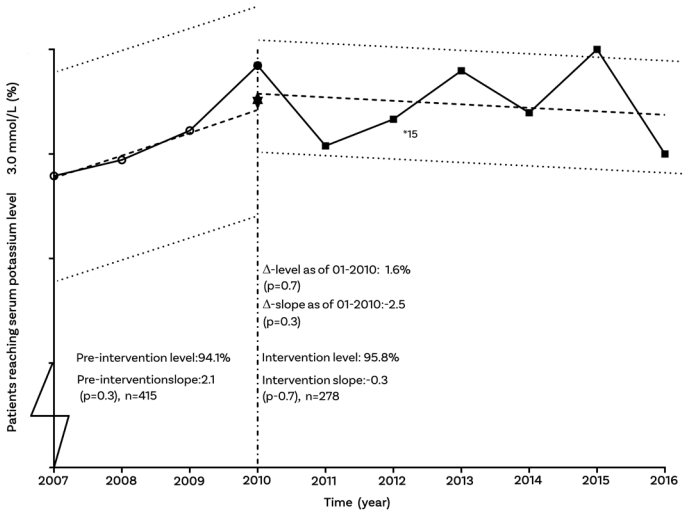


FIGURE 2. *A-B Graphical representation of the data points and segmented regressions using inverse variance-weight per 12-month period for percentage of patients prescribed potassium supplementation (Panel A) and time to prescription of potassium supplementation (Panel B). On the X-axis, time is shown; on the Y- axis, the respective endpoints. Open circles represent the individual data points pre-intervention, and filled black squares represent the individual data points in the intervention phase. The striped line to the left of the vertical dotted-striped line represents the model for regression in the pre-intervention phase, and the striped line to the right represents the model in the intervention phase. The dotted lines represent the corresponding 95% confidence intervals for the levels, excluding uncertainty of the slope. Stars (*) and the succeeding numbers represent data points not meeting EPOC guideline for 20 observations per data point; the numbers provide the number of observations in the given data point.*

A. Percentage patients reaching mild hypokalemia, SPL ≥ 3.0 mmol/L



B. Time to reach mild hypokalemia SPL ≥ 3.0 mmol/L

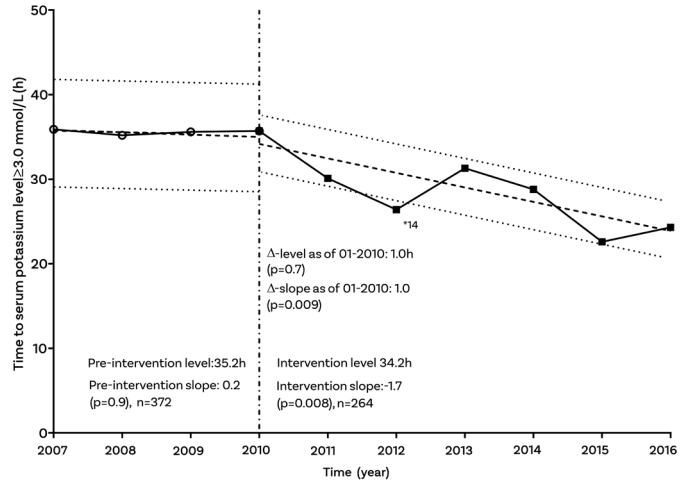
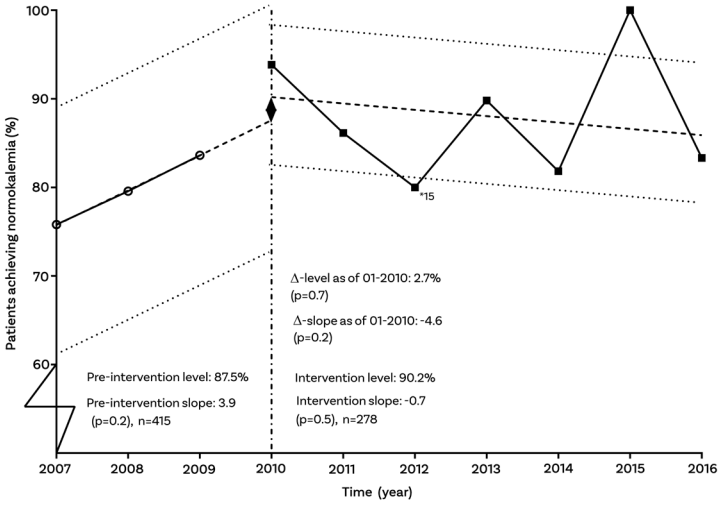


FIGURE 3. *A-B graphical representation of the data points and segmented regressions using inverse variance-weight per 12-month period for percentage of patients reaching mild hypokalemia, SPL ≥ 3.0 mmol/L (Panel A), and time to reaching mild hypokalemia (Panel B). On the X-axis, time is shown; on the Y- axis, the respective endpoints. Open circles represent the individual data points pre-intervention, and filled black squares represent the individual data points in the intervention phase. The striped line to the left of the vertical dotted-striped line represents the model for regression in the pre-intervention phase, and the striped line to the right represents the model in the intervention phase. The dotted lines represent the corresponding 95% confidence intervals for the levels, excluding uncertainty of the slope. Stars (*) and the succeeding numbers represent data points not meeting the EPOC guideline for 20 observations per data point; the numbers provide the number of observations in the given data point.*

A. Percentage patients reaching normokalemia during hospitalization



B. Time to normokalemia

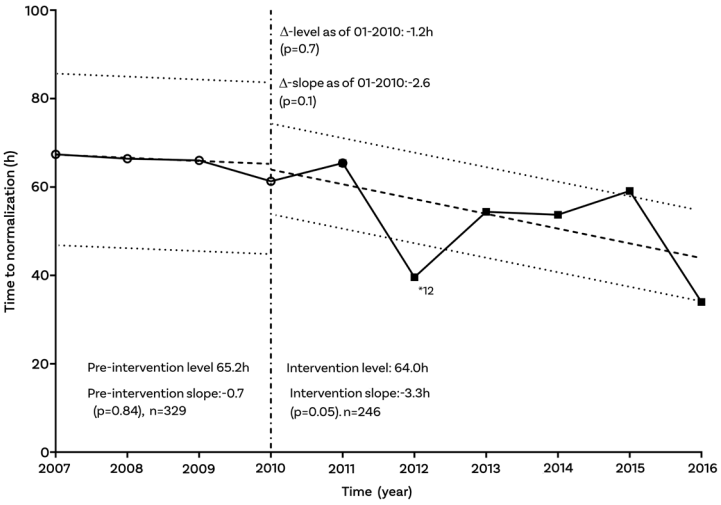


FIGURE 4.A-B *Graphical representation of the data points and segmented regressions using inverse variance-weight per 12-month period for percentage of patients reaching normokalemia (Panel A) and time to reach normokalemia (Panel B). On the X-axis is time; on the Y-axis, the respective endpoints. Open circles represent the individual data points pre-intervention, and filled black squares represent the individual data points in the intervention phase. The striped line to the left of the vertical dotted-striped line represents the model for regression in the pre-intervention phase, and the striped line to the right represents the model in the intervention phase. The dotted lines represent the corresponding 95% confidence intervals for the levels, excluding uncertainty of the slope. Stars (*) and the succeeding numbers represent data points not meeting the EPOC guideline for 20 observations per data point; the numbers provide the number of observations in the given data point.*

Total duration of hospitalization

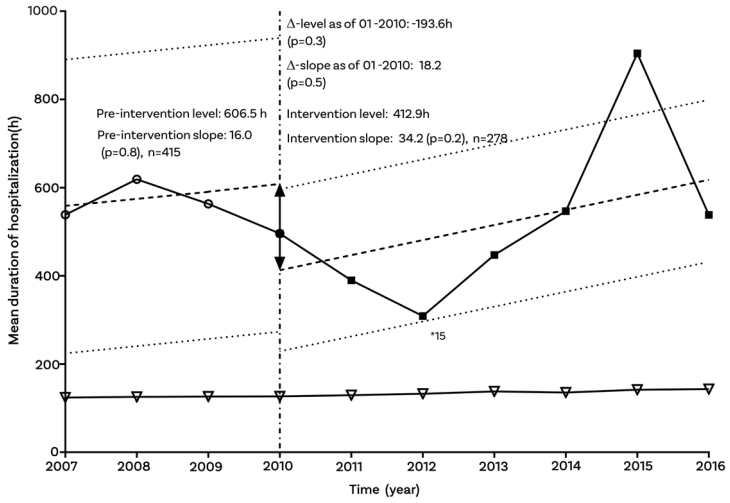


FIGURE 5. *Graphical representation of the data points and segmented regressions using inverse variance-weight per 12-month period for total duration of hospitalization. Open circles represent the individual data points pre-intervention, and filled black squares represent the individual data points in the intervention phase. The open rectangles represent the mean hospitalization times for control patients without SPL <2.9 mmol/L during hospitalization. The striped line to the left of the vertical dotted-striped line represents the model for regression in the pre-intervention phase, and the striped line to the right represents the model in the intervention phase. The dotted lines represent the corresponding 95% confidence intervals for the levels, excluding uncertainty of the slope. Stars (*) and the succeeding numbers represent data points not meeting the EPOC guideline for 20 observations per data point; the numbers provide the number of observations in the given data point.*

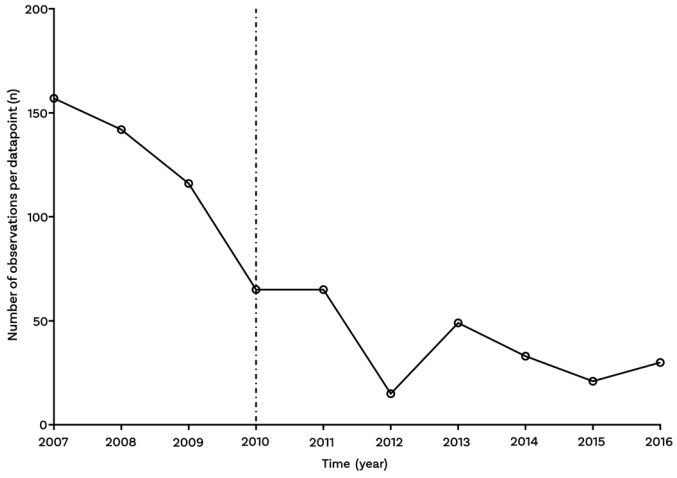


FIGURE 6. *Graphical representation of the number of observations per data point included in the analysis. On the X-axis is time; on the Y- axis, the number of observations.*

DISCUSSION

This study demonstrated a positive effect of the clinical rule-based pharmacists' intervention on the percentage of patients for whom potassium supplementation was initiated during hospitalization, time needed to initiate this treatment, and time to achieve mild hypokalemia. Nevertheless, this study did not demonstrate improvement in percentage of patients reaching normokalemia or time to reach normokalemia and only showed a trend toward shorter hospitalization.

Failure to improve percentage of patients normalizing and time to normalize SPL is in contrast with the study performed by Paltiel *et al.*.[17] A possible explanation for these contrasting results could be the differences in baseline and approach to treating SPL <2.9 mmol/L. In our study, a high percentage of patients—87.5%—already reached normokalemia during hospitalization at baseline compared to 70–75% in other studies.[17,32] Baseline response rate and time could also have been underestimated in our study, as only electronic orders were used to measure them. Improvement in time to mild hypokalemia but not time to normokalemia suggests a different approach to treating hypokalemia compared to the study performed by Paltiel *et al.*.[17] It is also possible that the advice regarding potassium supplementation dose was too conservative to improve time to reach normokalemia.

Total duration of hospitalization was not significantly reduced despite a clinically significant reduction of hospitalization by 8.1 days, or more than 32.0%. This result is in contrast to an earlier study by Tate *et al.*, which found a significant decrease in hospitalization duration.[22] A possible explanation for this is the small number of data points in the pre-intervention phase, which creates a sizable confidence interval for duration of hospitalization. Additionally, the long mean hospitalization duration compared to the control population and the literature suggests that in our study population, severe hypokalemia is likely to be a symptom of severe illness instead of e.g. overdosing a loop diuretic. Therefore, hypokalemia probably only plays a partial role in total hospitalization time.

To our knowledge, this is the longest study to evaluate the effect of a clinical rule-based intervention over time. It is also the first study to use a time series analysis to study the effect of such an intervention. Using a time series analysis corrects for non-stationary means, which could have led to false positive conclusions in earlier studies.[33] The study did not fully meet the recommended criterion of at least 20 observations per data point to attain an acceptable level of variability.[34] One data point, the year 2012, consisted of 15 observations. Nevertheless, no significant difference was observed in the regressions including or excluding this specific data point. Consequently, we assumed that an acceptable level of variability was achieved. The number of observations over time decreased, as seen in Figure 6, causing a large fluctuation in means during the intervention period. The decreasing number of patients could be explained as an effect of the intervention itself or as a sign of overall improvement in care, indicating that hypokalemia is noticed and treated at an earlier stage.

One of the limitations of this study was its retrospective design. While inferior to prospective design in respect to data collection, preventing bias and so on, ITS design has been accepted as one of the best alternatives in cases where trial design is not an option. Another limitation to this study is not including clinical findings, observed symptoms, EKG findings and cardiac events. Moreover, the current once daily approach can cause significant lag time if SPL is not routinely measured. One option to overcome this limitation is increasing the number of CDS system runs. However, the collected data suggest that the benefit would be minimal because, due to the urgency of the request, response rate and time to stat laboratory orders were already very rapid.

The aim of studying this intervention was to test if the approach could effectuate an improvement in response time to critical care values in individual patients while minimizing alert fatigue and frustration. While the latter two were not directly measured, a periodic evaluation was performed as part of the regular plan-do-check-act (PDCA) cycle.[35] Among other reasons, physicians positively assessed the intervention because of the negligible number of times they were called. An average of 1.2 calls per week were placed to approximately 20 resident physicians directly involved in clinical care. Acceptance rate was 88%. Based on these evaluations, the hypokalemia clinical rule was expanded and other clinical rules were added monitoring response to critical care values.

CONCLUSION

Implementation of a clinical rule-guided pharmacists' intervention is possible and produced improvement in response rate and time to prescription. Improvement in time to achieve mild hypokalemia suggests that improvement in response rate and time to prescription resulted in measurable improvement in correction of serum level potassium. However, no significant effect was found on percentage and time to normokalemia or duration of hospitalization.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found at:
https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fjcpt.13101&file=jcpt13101-sup-0001-Appendix.docx

Or by scanning the QR code:

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4

GENERAL DISCUSSION

GENERAL DISCUSSION

INTRODUCTION

Adverse events in healthcare are one of the ten leading causes of death and disability worldwide,[1] and more than half of them are preventable.[2] Adverse drug events (ADEs) are responsible for 19% of adverse events. In past decades much effort has been placed into digitizing healthcare. However, despite these efforts, high rates of preventable ADEs persist.[3,4] Many types of medication errors disappeared following digitalization. However, digitalization also introduced new types of medication errors like alert fatigue.[5,6] The most significant reason for the high override rate is the lack of contextualization in CDS systems.[7-10] This thesis aimed to investigate whether incorporating context into CDS systems could help improve the detection and prevention of ADEs.

This general discussion chapter places the thesis findings into the broader perspective of detecting or preventing adverse drug events by discussing the themes that emerged during the execution of this study. The following three main topics are discussed:

- Preventability of ADEs and knowledge implementation
- Using alerts to prevent ADEs
- Deep learning CDS models

The discussion includes recommendations based on the research findings. Directions for further research are also proposed.

PREVENTABILITY OF ADVERSE DRUG EVENTS AND KNOWLEDGE IMPLEMENTATION

The final part of **Chapter 1.2** focused on translating knowledge into clinical rules, and implementing and validating them. However, as discussed in that chapter, a Plan-Do-Check-Act cycle is necessary to monitor performance continuously and refine clinical rules, raising several questions, including why this is the case and whether new bugs are found in the software programming daily, healthcare professionals have started to use EHRs differently, or other factors are involved.

Shifting of what is known

Despite the widespread introduction of EHRs, CPOEs, and CDS systems in past decades, the preventable adverse drug event (ADE) rate has not declined.[4] When analyzing this problem, it should be noted that the term preventable is constantly shifting. What seemed to be a previously unexplained or unknown adverse drug reaction (ADR) a decade ago may now have a known cause. An example of such a shift is the discovery of the significant role of the CYP2C19 phenotype in therapy failure of clopidogrel. Until a decade ago, recurrent strokes while taking clopidogrel were considered type F adverse drug reactions (failure of therapy). Currently, such an event has shifted toward being a preventable ADE.

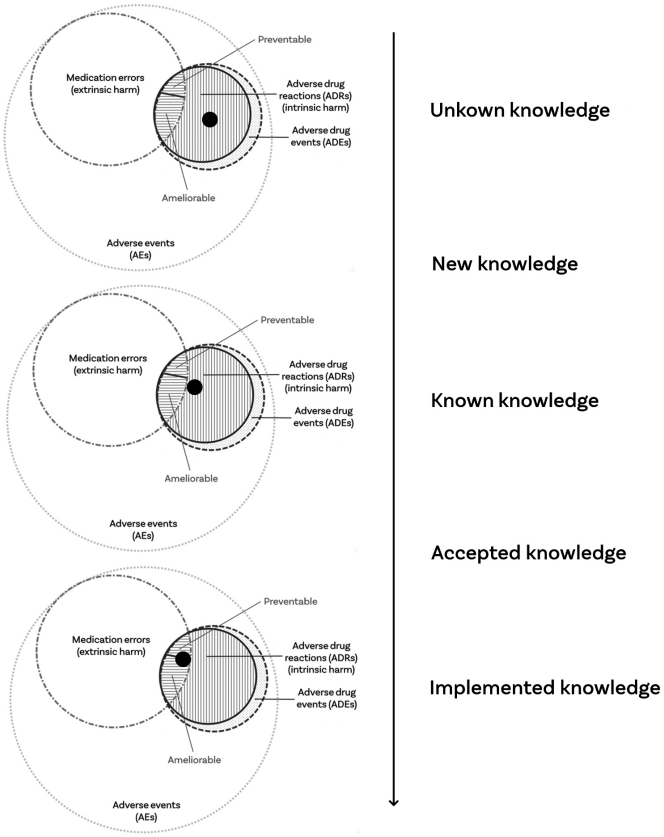

FIGURE 1. *Multiple Venn diagrams illustrating shifts in categorizing adverse drug reactions (ADRs) as adverse drug events (ADEs) with an increasing body of knowledge. The black dot represents knowledge of the first unknown shift in time toward a preventable ADE. For example, the significant role of the CYP2C19 phenotype in therapy failure of clopidogrel was unknown during the drug's introduction in 1998. Clopidogrel therapy failure in patients with CYP2C19 PM and IM phenotypes slowly shifted toward implemented knowledge incorporated into more guidelines determining phenotypes before or during clopidogrel therapy.*

Applying this fact to Morimoto *et al.*'s Venn diagram (Figure 1) reveals that the circle of previously unexplained or unknown ADRs (intrinsic harm) increasingly overlaps the circle of medication errors, becoming extrinsic harm. Several factors drive this shift. First, medical knowledge is increasing exponentially.[11] In 1993, PubMed® counted approximately 8,000 publications annually. By 2003, this figure had doubled, while in 2020, it rose to over 110,000 publications annually, a 1,375% increase in 27 years. The expectation is that big data and artificial intelligence will increase this even further. For a neurologist, as used in the example, the number of newly published randomized clinical trials comes down to 16 daily. Second, the exponential increase in medical knowledge is accompanied by growing possibilities in medicine. Four decades ago, low dose of aspirin or a coumarin was the only option for

preventing a secondary stroke. Currently, physicians have half a dozen possible medication, dosage, and combination possibilities, depending on risk factors, comorbidities, and co-medication. Third, before the introduction of EHRs and easy digital exchange of medical records and data, a healthcare provider could claim not to know part of a patient's history or results; currently, most information is only a mouse click away.

Knowledge implementation

While medical knowledge grows exponentially, healthcare professionals struggle to keep up. Such a struggle is inevitable if healthcare professionals must read and maintain 16 articles daily. Healthcare professionals are only expected to act on new knowledge when it is incorporated into clinical practice guidelines. An unknown ADE then directly shifts to also being a medication error because regulators and colleagues expect compliance with existing guidelines from that moment.

However, medical guidelines are only revised once every 3–10 years.[12-14] Once such a guideline is revised, translating it to clinical practice can easily take another five years. Consequently, it can take up to 15 years for medical knowledge to be widely implemented.[14]

The fact that guidelines are updated only every 3–10 years is concerning. The process can be significantly accelerated only by using international clinical networks. An example of a CDS based on a commercial clinical network is the widely used UpToDate®, where experts constantly update and translate knowledge to clinical practice, making information on the best and most proven diagnostic tools and treatments readily accessible.

Recommendation: stop using traditional clinical practice guidelines and use dynamically updated clinical networks.

Accelerating knowledge use in practice

Freely available, dynamically updated clinical networks can accelerate knowledge implementation substantially: in 3–10 years. However, this does not solve the problem of maintaining and using the knowledge from clinical networks in daily practice. It is still hard to imagine that a healthcare provider will read the relevant topic whenever they see a new patient. A solution would be to transfer such knowledge directly and dynamically into clinical rules as input for CDS systems, again reducing the time to implement new medical knowledge by five years.

Recommendation: make clinical network knowledge directly available during patient treatment.

The question is how to accomplish this. It requires, possibly automatically, programming clinical rules used in CDS systems advising the next step in diagnosis or treatment and warning practitioners when they deviate from this evidence-based medicine path.

Recommendation: translate knowledge from clinical networks directly into clinical rules usable in clinical practice.

Designing clinical rules to be interoperable and sharable

As discussed in the general introduction, implementing, designing, and keeping clinical rules up to date for one hospital, or even one country, is a massive time and money-consuming task only the big few can undertake[15] and is one of the reasons CDS system adaptation in hospitals proceeds very slowly. A survey sent to all Dutch hospital pharmacies in 2015 revealed that only 48% use some form of CDS system.[16] In 2007, Simon *et al.* observed the same trend across the U.S.A., where most EHR implementations employed little or no decision support.[17] Therefore, it is vital that medical knowledge in the form of clinical rules is centrally maintained, interoperable, and sharable. This concept would allow clinical rules to be externally maintained, making a significant leap in the efficacy of development and maintenance, and should work in "such a way that healthcare organizations and practices can implement new state-of-the-art clinical rules with little or no extra effort on their part."[15]

Recommendation: make clinical rules interoperable and sharable.

An example, the CRISP project

During our 2015 research (the CRISP project), we undertook a project to jointly develop a CDS system across three different hospitals using three different EHRs. This study resulted in, among others, a model for clinical rules to retain a high level of specificity while maintaining flexibility and interoperability.

The clinical rules were given three levels, so-called master levels, and an indefinite number of sublevels, in addition to the three-level approach used in the GuideLine Interchange Format (GLIF) architecture. Figure 2 presents a graphic representation of the three-level clinical rule model. All three master levels were designed to be readable and interpretable by clinicians and experts in the same way as a regular clinical practice guideline. The highest of the three levels is called the master rule level or level 1. All terminology at this level uses standardized clinical terms. For example, when asking the question, "Does the patient currently have heart failure?" ICD-10 I50 is used. ATC M01 selects patients taking nonsteroidal anti-inflammatory drugs (NSAIDs). Levels 2 and 3 translate system-specific or institution-specific terminology into standardized clinical terms usable in level 1. When possible, a thesaurus is used to translate terms. However, this was not possible in some cases because no translation was readily available or no scientific consensus had been reached regarding a clinical term. Moreover, information must be derived from other available data in some situations. For example, enteral feeding tube use could be derived from the current tube feeding product on the drug list and translated to the standardized clinical term for enteral feeding tube use. In another system, the free text entered into a

medication order instructing the nurse to crush a tablet and flush through the feeding tube was mined. In many cases, a combination of factors confirmed a patient's state or disease not coded in standardized clinical terms.

The level 2 and level 3 sublevel rules are similar to the level 1 rules, with the exception that they use EHR or institution-specific terminology in addition to standardized clinical terms. For example, an exception is made in the master clinical rule for intensive care unit (ICU) patients. However, the source information system database does not mention an ICU ward because only geographical locations are entered. Therefore, the ICU was known as C4A because it was located in wing C, level 4, side A of the building. Moreover, beds 1–6 are critical care beds, and beds 7–14 are medium care beds, which are also not coded or labeled in the EHR database. The level 3 flowchart labels patients of the respective medical center, on ward C4A, in beds 1–6, as ICU patients.

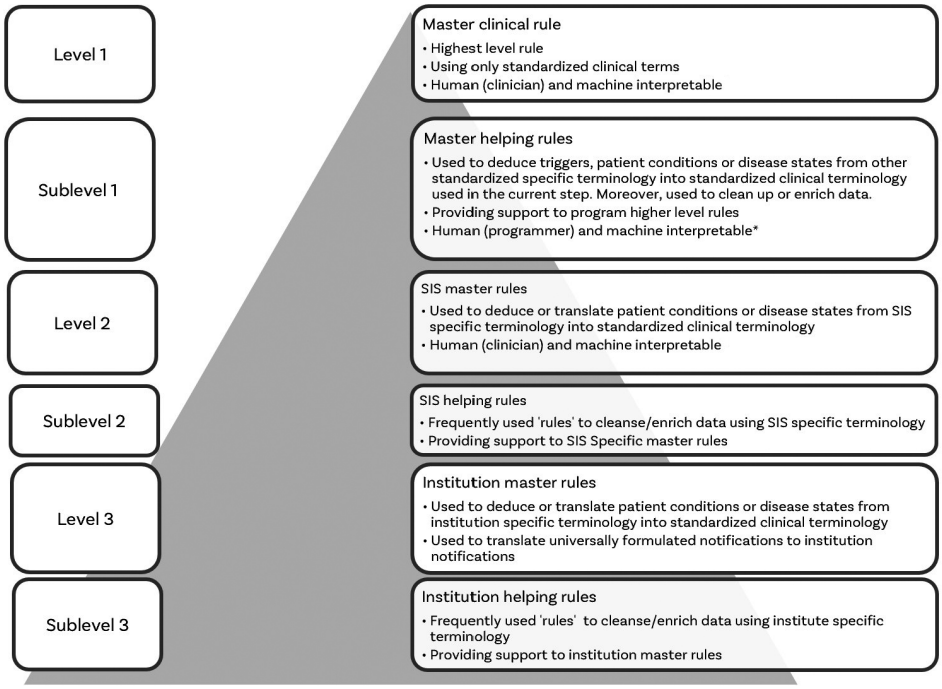

FIGURE 2. *A graphic representation of the model used to design and program clinical rules in the CRISP project. SIS: Source information systems; CRISP: Clinical rules in Santeon Project*

Besides such simple translations, the institution-specific rules (level 3) are also designed to customize advice to the current ward or medical center. For example, the expert team agrees that patients should start a prophylactic proton pump inhibitor (PPI) dose in a particular situation. A list of accepted PPIs and doses is also added to the clinical rule.

However, the master rule does not specify which PPI should be used. Therefore, medical center A could decide to prescribe omeprazole and medical center B pantoprazole. The preset medication order in center A advises 20 mg of omeprazole once daily at 07:00, while the notification in center B displays the advice to order 20 mg of pantoprazole once daily at 18:00.

Recommendation: design layered clinical rules that are flexible and usable in multiple settings.

From CDS systems and clinical rules to humans handling alerts and advice

Implementing a state-of-the-art CDS system with clinical rules dynamically updated using clinical networks does not guarantee a reduction in preventable ADEs. Gordo *et al.* 2021 demonstrated that most ADEs are caused by medication errors due to human failure to follow guidelines and or CDS advice.[18] Thus, many clinical rules can be built, but if the advice given in them is ignored, there is still no guarantee of implementing new medical knowledge in practice and preventing many ADEs. If CDS advice helps practitioners adhere to clinical guidelines or manage, for example, drug–drug interactions, why is it ignored?

USING CDS ALERTS TO PREVENT ADES

Chapter 1.2 provided an overview of different CDS systems, examining the different types of communications, such as passive or active alerting and consulting or critiquing. Since most current CDS systems use active critiquing alerting, this section focuses on alerts issued by such CDS systems. More sophisticated artificial intelligence models are discussed in the third topic of this chapter.

Introduction to alerts

From a human–computer interaction perspective, an alert, error, warning, or alarm is "a way of a system to attract the user's attention to significant, abnormal or threatening situations to ongoing pending or future tasks."[19] In healthcare, the term alert has emerged in computer use since the move from passive to active CDS systems. Following attention to adverse events and the introduction of EHRs and CPOEs, the number of alerts received by healthcare professionals has increased exponentially.[20,21] Although alerts can help prevent healthcare professionals from making mistakes, such as prescribing a drug to a patient who is allergic to it, such alerts have also introduced several new problems.[5,6]

The problem with alerts

Independent of the field of application, aviation, naval, or consumer mobile use all seem to have been burdened with the ills of alerts. Within the healthcare domain, the alert burden has one of three different origins:

- Wrong timing: interruptions from alerts often cause errors.
- Wrong messages: routines for handling multiple simultaneous alerts are inadequate.
- Irrelevant messages: false alarms or known alerts create a “cry-wolf” effect or alert fatigue.

The subsequent part of this general discussion topic is dedicated to alert fatigue.

Psychology and physiology of alert fatigue

Habituation

Alert fatigue is one of the top ten safety concerns in hospitals.[22] The sheer number of alerts causes healthcare professionals to mentally shut out overwhelming alerts, leading to override rates as high as 49-95%.[23-29] The reason for these override rates is habituation, also called normalization or desensitization.[30] Habituation occurs when individuals begin to tolerate, normalize, and ignore stimuli the more they are exposed to them, “just like the endless beeps on your smartphone.”[31] Habituation is promoted when a reward or punishment is associated with a stimulus, as with medication alerts. Habituation is a form of non-associative learning, defined as “a process in which an organism’s behavior toward a specific stimulus changes over time without any evident link to (association with) consequences or other stimuli that would induce such change.”[32]

Why habituation occurs

Several theories explain why habituation occurs. The main two are comparator theory and dual-factor theory. Comparator theory suggests that the brain creates a model of the expected stimulus, as in machine or deep learning. With frequent presentations, the stimulus is compared to the model, and if it matches, the response is inhibited. Dual-factor theory suggests that the brain compares the stimulus to other stimuli to choose where to focus attention.

Factors influencing habituation

Several factors influence how quickly individuals become habituated to a stimulus. The key habituation factors are change, duration, intensity, and frequency.[33] Although the first two cannot be changed in medication alerting, the last two can be changed. For example, intensity can be changed by highlighting alert levels in different colors. However, the colored alerts are eventually overwhelmed by the frequency of alerts. Medication alert response drops 30% for each repetition generated.[30] Therefore, it seems that the only solution to overcoming alert fatigue is reducing the number of alerts.

Recommendation/statement: *reducing the number of medication alerts is the only way to reduce alert fatigue.*

Reducing the number of alerts using context

Previous studies have demonstrated that there is little or no room and consensus to safely turn off drug-drug interaction alerts, using conventional suppression.[34,35] When evaluating attempts to reduce medication alerts, it becomes evident that the most significant unused factor is the alert's context. As discussed in the introduction, a lack of contextualization in CDS systems is one of the most significant reasons for high override rates. In computer science, context refers to the idea that a system is capable of sensing and reacting based on its environment. Dey's definition of context is frequently cited in the wider literature: "Context is any information that can be used to characterize the situation of an entity. An entity is a person, place, or object considered relevant to the interaction between a user and an application, including the user and applications themselves." Based on this definition, a CDS system providing context attempts to make assumptions about the current situation's relevance, depending on the user's task.[36] Reducing medication alerts from the habituation perspective implies that alerts should only be presented if they are actionable. Moreover, they should only be presented when they match the healthcare provider's workflow; otherwise, interruptions from alerts frequently cause errors. In other words, the patient's status and the healthcare provider's task should be considered. These two contexts are described and applied in **Chapter 3.1** as clinical context and workflow context. Other studies also concluded that CDS systems should have greater flexibility to customize alerting, notably by adding contextual modulation, also called specificity modulation.[37-39] The term contextual modulation derives from neurobiology: the change in the neurons' responsiveness to a stimulus caused by context, denoting a decrease in habituation if used correctly.[40]

Recommendation: Make CDS systems and clinical rules more context-aware.
Recommendation: Use contextual modulators only to show alerts when actionable in a specific case.
Recommendation: Show alerts depending on the workflow context; in other words, when the healthcare provider is open to receiving the advice and acting accordingly.

Types of context

Clinical context

Chapter 3.1 describes two forms of context studied to reduce the number of DDI alerts for pharmacists and pharmacy technicians in a hospital setting. Based on the results, most DDI alerts are easy to suppress by incorporating clinical contextual modulators without losing essential alerts. Furthermore, the intelligence and data required to suppress most alerts are easily accessible, and concepts are easily extrapolated to other clinical settings. The same is true for alerts concerning laboratory results, such as hypokalemia. **Chapter 3.1**

demonstrates that hypokalemia alerting can be very specific, reducing the number of alerts or calls on this subject by more than 95%.

Recommendation: Use clinical context to improve alert actionability.

Workflow context

Presenting advice to the right healthcare professional. Following the dual-factor theory of habituation, some DDI alerts should not be presented to prescribers because, at that moment, they consider them a second-order problem. The best example of this is absorption time-dependent DDIs. Most physicians consider the timing of drug use a second-order problem. Similarly, most hospital pharmacists consider this a problem that can or should be solved by a pharmacy technician and a nurse together.[29,41] Hence, it is not only the timing of an alert that is important. Perhaps more important is who receives the alert, specifically a healthcare professional tasked with managing such alerts.

Recommendation: Make DDI alerts visible only to healthcare professionals that act on them.

Incorporating previous actions – alert management. Current decision tree-based CDS models do not remember previous alert management as learning models would. Therefore, healthcare professionals are frequently presented with DDI alerts multiple times, virtually illustrating Einstein's definition of insanity. **Chapter 3.1** also considers this aspect. If a DDI was previously managed and deemed irrelevant, the CDS system could remember this. Medication orders can be changed at many different points. However, if no changes are made in the dose of one of both drugs, no change in the DDI result is expected. In addition to medication order changes, contextual factors can change. Both were considered. Adding this type of workflow context proved to be the biggest contribution to suppressing irrelevant DDI alerts, decreasing the number of alerts by almost 40%. This study demonstrates the importance of incorporating alert management into CDS systems, ensuring no unnecessary alerts are shown again and monitoring the result. The CDS system can also monitor intervention follow-up.[41,42]

Recommendation: Allow the CDS system to check the follow-up of alert advice.
Recommendation: Software suppliers should be encouraged to make DDI alerts visible only when changing doses OR if important clinical context changes have occurred.

Critiquing model versus advising model. So far, the alert part of the general discussion has focused on the critiquing model using alerts, including the pitfalls of alert fatigue. However, another possible solution to overcoming the problem of alert fatigue is moving some of

the clinical rules to an advising model for prescribers. This model is much less studied.[43] Possibly the best-known examples are integrated CDS system dosing guidance.[44,45] For example, Cox *et al.* compared a CDS system guiding prescribers regarding the correct dose of aminoglycoside versus close monitoring (CDS-assisted) by clinical pharmacists and obtained improved results using the advising CDS.[45] Therefore, instead of a CDS system raising an alert stating, "BEEP. You are possibly doing it wrong," the alert could state, "Based on the patient's diagnosis, weight, renal function, and pharmacogenetic profile, we propose prescribing dose X. Click here to accept." However, much simpler decision support can also be provided using smart or standardized order sets within the CPOE incorporating common situations.[46] For example,

- Ciprofloxacin 1x day 500 mg oral; ordinary infection (restricted-use antibiotic); eGFR < 30 ml/min
- Ciprofloxacin 2x day 500 mg oral; ordinary infection (restricted-use antibiotic); eGFR > 30 ml/min
- Ciprofloxacin 2x day 750 mg oral; diabetic foot (first-choice antibiotic); eGFR > 30 ml/min
- Ciprofloxacin 1x day 750 mg oral; diabetic foot (first-choice antibiotic); eGFR < 30 ml/min

Such relatively simple standardized order sets can effectively decrease mortality and cost by allowing prescribers to choose the correct drug or drug set easily, preventing common dosing errors and time-dependent drug-drug interactions.[47] The greatest disadvantage of using simple, standardized order sets is that only a certain number of contextual modulators can be incorporated. The higher the number of contextual modulators the more combinations and standardized order sets are needed, making the correct standardized order much harder to find, with the risk of choosing the wrong drug or dose. Therefore, it would be advantageous to directly guide a prescriber toward the correct dose based on all contextual modulators[45] and, possibly better still, to directly incorporate these in pharmacokinetic and dynamic models (PKPD) predicting exposure, as in Roggeveen *et al.* 2020.[48]

Recommendation: more research should be devoted to developing and testing advising CDS models. Until then, healthcare providers should invest time in implementing standardized order sets.

Incorporating CDS systems into clinical workflows. As discussed in the previous paragraph, using advisory models in straightforward triggers, starting medication, is relatively simple. The question is how to incorporate alerts triggered by changes in dynamic patient parameters or laboratory results. Adapting a CDS system to clinical workflows significantly increases the

probability that alert advice will be read and followed.[49] For clinical pharmacists, a dynamic to-do list usually suffices. However, for clinicians such as intensivists, such outputs do not fit into clinical workflows. Therefore, other ways of raising the alert should be explored. One of the more recent attempts to incorporate CDS systems into clinical workflows was to include CDS system advice in checklists frequently used in ward rounds.[50] An example of such a system is Tracebook. This dynamic checklist is process-oriented and context-aware, demonstrating great promise and user acceptability.[51]

Recommendation: more research and efforts by software vendors should be devoted to better fitting alerts into the clinical workflows of healthcare professionals.

However, not all types of alerts can or should wait until the next ward round. For example, severe hypokalemia, as discussed in **Chapter 3.2**, should be treated immediately. In cases where immediate treatment is required and has not been started, a pop-up or text message would be the preferred alert method. The same is true for several types of DDIs. For example, starting meropenem in a patient using valproic acid should generate an immediate stop. While combining a RAASi with a potassium-sparing diuretic would only require a critiquing alert should serum potassium not be ordered within a week.

Recommendation: when designing clinical rules, careful thought should be given to the moment when action is required by the healthcare professional, depending on contextual modulators and the severity of the situation.

DEEP LEARNING CDS MODELS

Chapter 1.2 discussed several fundamental CDS system characteristics. However, the models used within a CDS were not discussed within the domain of artificial intelligence (AI). All the chapters of this thesis describe rule-based models. While rule-based CDS systems are becoming more common, adapting and using machine learning models, such as those described and predicted by Maxmen in 1976 in his book, *The Post-physician Era: Medicine in the 21st Century*, still seem remote.[52] This final section of the general discussion is dedicated to positing rule-based CDS systems compared to the upcoming and highly anticipated deep-learning CDS systems.

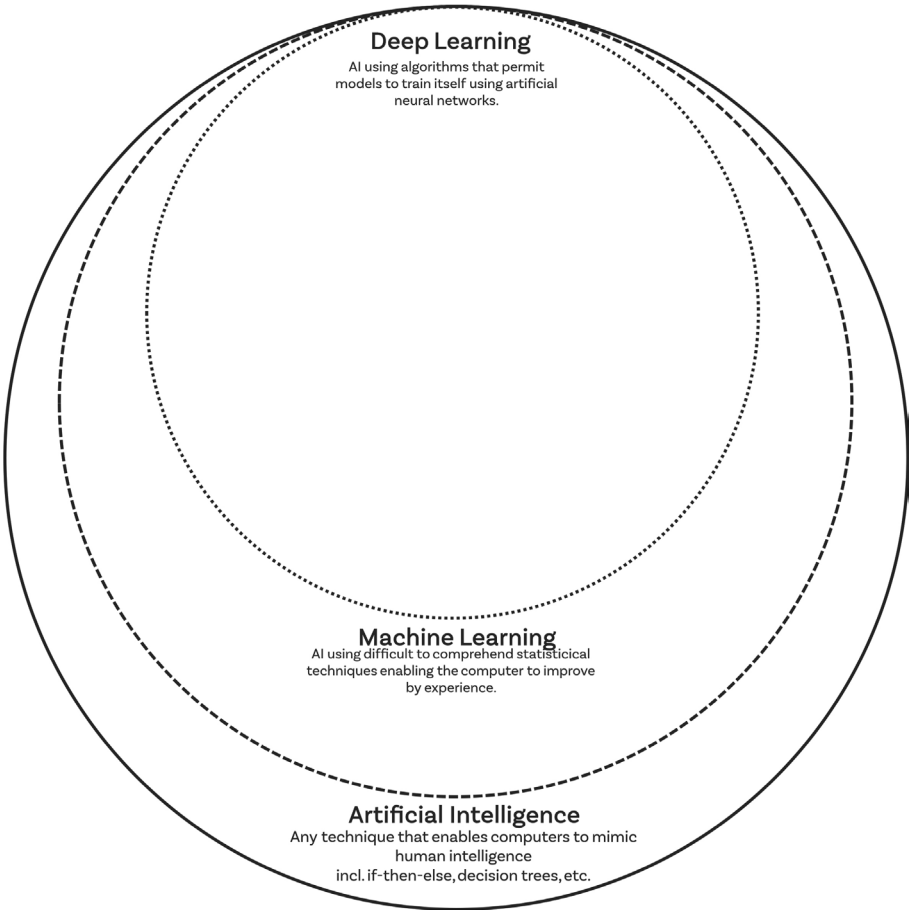

FIGURE 3. *Venn diagram illustrating the relationship between artificial intelligence (AI), machine learning, and deep learning.*

Introduction to artificial intelligence (AI)

Before diving deeper into the topic of deep learning, it is crucial to understand the definitions of different types of AI and their underlying techniques. Figure 3 presents a Venn diagram depicting the relationship between different AI techniques. AI is the collective name for all techniques and models that enable computers to mimic human intelligence, including rule-based models to automate parts of healthcare professionals' clinical reasoning. Machine learning goes a step further; it uses complicated statistical models to refine its programming, improving the alert-to-noise ratio by, for example, automatically hiding alerts based on the previous management of alerts with similar metadata characteristics. An example is not showing oxycodone and citalopram drug–drug interaction alerts because most previous alerts in similar situations were overridden within seconds.

Deep learning is a subset of machine learning which extends beyond machine learning; it uses multilayered artificial neural networks (ANNs), which can be used to model multiway interactions. Artificial neural networks (ANNs) are algorithms inspired by the biological neural networks that constitute animal, including human, brains. An ANN is based on a collection of connected nodes called artificial neurons. An artificial neuron receives a signal, processes it, and can signal neurons connected to it. Multilayered ANNs are aggregated into layers. Increasing connections between neurons is largely based on previous data, also called training sets, allowing the algorithm to make decisions or predictions for future cases. For example, patient A is likely to develop an ADR to drug X if factors one, two, three and four are present, based on the occurrence of factors one to four in previous sets.

Deep learning

The most studied and applied deep learning model uses supervised learning. Compared to unsupervised learning, supervised learning requires tagged data as a training set. Although common in gaming reinforcement, learning in healthcare is in its infancy. It is a model that can virtually mimic a healthcare professional and make decisions based on previous data, order tests, and start treatments to improve treatment prognoses.

In previous years, ANNs have proven themselves in image-intensive fields.[53,54] Rapid development in this field of medicine can be explained by two significant factors. The first is that ANNs, like the human brain, are perfectly capable of processing visual data. The second is that image-intensive medical fields have fewer inputs. For example, to diagnose a specific area of the skin, the ANN input is one or multiple pictures of the skin, after which the model will decide if that specific area of the skin is benign or malignant. Pathology images can be added to make the model more complex. Training such an ANN is also relatively easy, using outcomes as the gold standard (supervised learning).

Other fields of medicine, such as internal medicine, currently base a significant part of the input on untagged data, including the patient's medical history, an impression of the patient, and a physical examination. Such data can be partially tagged, for example, for a stomach ache, localization, the type of pain, pain duration, and pain score. However, current EHRs do not support such extensive tagging possibilities, and physicians are reluctant to spend time tagging all the variables. What stands out is that thousands of inputs exist when examining such a case for ANNs. Hence the number of connections to be trained is billions.

Placing deep learning into an example

This section examines the possibilities in pharmacotherapy using drug–drug interactions as an example. A deep learning model could be tasked with discovering new DDIs or improving alerting and managing known DDIs.

Each DDI has several characteristics to consider during evaluation. An example is drugs that increase the risk of serotonin syndrome, an ADR with a presumed incidence somewhere

between 0.09–0.17% when combining high-risk drugs. Training an ANN to identify patients at risk of developing serotonin syndrome would require thousands or hundreds of thousands of cases and millions of negative cases. Since little is known regarding which factors increase the risk of serotonin syndrome, it is also difficult to predict whether the ANN is provided with the required tagged information to correctly identify the patient at risk. However, it is not impossible. Improvements in training ANNs, such as federated learning and systems, which automatically tag free text during input in EHRs, can solve the abovementioned issues in the future.

Trust issues regarding (deep) learning models

Perhaps one of the most significant reasons for the relatively slow acceptance and implementation of deep learning models concerns the trust issues regarding such ANNs. Trusting an ANN is problematic if the data or science on which its conclusion is based is unknown, prompting the question of whether it can be easily explained or visualized. Deep neural networks use (hidden) "layers of learned nonlinear features to model a huge number of complicated but weak regularities within the data." It would be unimaginable for a human being to understand the different interactions between all the features of such a complex ANN, prompting the question of how this is different from trusting, for example, self-driving cars placing human lives in the hands of an ANN. In my opinion, it is at least possible to see how the car is driving itself based on the same visual data. The ANN's performance can therefore be rated based on how it performs in a given situation slowly earning trust. In medicine, decisions and consequences are far removed, sometimes by years. Therefore, it is more challenging to begin trusting an ANN to, for example, choose and dose neo-adjuvant chemotherapy in patients, only to assess recurrence rates years later.

Accepting black box technology

As discussed in the previous paragraph, it is impossible for a human to interpret all the features of deep learning ANNs. Consequently, why the system suggests a particular diagnosis or therapy will never be understood. Therefore, it is vital to prove that an AI system outperforms the experts as in image-intensive fields of medicine such as radiology, radiotherapy, pathology, ophthalmology, and dermatology. In other fields of medicine, randomized clinical trials will be necessary to prove that the algorithm outperforms humans, presenting a new problem: deep learning algorithms are not static. A potential solution is a three-step model proposed by Price *et al.* 2018. Step one is procedural: proving that the algorithm is developed according to well-vetted techniques and trained using high-quality data. In medicine, there is no need for a ChatGPT to tell confabulated stories. Step two determines whether the algorithm can reliably detect patterns. This process is easier for patterns already known to exist. However, it can be far more challenging to detect unknown patterns. Step three of the validation process continuously monitors failures

and successes. Therefore, continuously feeding the algorithm diverse, high-quality data is crucial.[55] However, obtaining diverse data is proving challenging; most currently developed algorithms are based solely on U.S. and European data, making outcomes inherently worse for non-Caucasians.[56] Diseases are expressed differently in other parts of the world, and individuals respond to therapies differently. Thus, context is key.

A pertinent question is whether ANN-based models will outperform and replace rule-based models over time. The likelihood is that they will do so in the future. However, research still requires several decades to conceive ways of using such models in medicine in an evidence-based manner, accept this black box technology, and devise regulations for using it. Until then, research should aim to apply as much context to current CDS systems as possible, optimally using evidence and technology to prevent harm or even save patients.

Statement: it will take several more decades for deep learning to be accepted and broadly used in healthcare to partially replace human decision-making.

CONCLUSION

This thesis aimed to investigate whether incorporating context into CDS systems could improve the detection and prevention of ADEs. It was demonstrated that adding context can help detect otherwise undetected potential ADEs. Moreover, it was demonstrated that context plays a pivotal role in decreasing the number of irrelevant alerts, making it much easier to prevent potential ADEs using the remaining relevant alerts. Healthcare professionals cannot make appropriate decisions purely based on a few facts; adequate context is needed. Consequently, a computer cannot be expected to provide suitable decision support without adequate context.

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5

SUMMARIES AND APPENDICES

CHAPTER 5.1

Summary

SUMMARY

Since the report “To Err is Human” was released, billions have been spent implementing electronic health records (EHRs), including often integrated computerized physician order entry (CPOE) and clinical decision support (CDS) systems. However, despite these efforts, high rates of preventable adverse drug events (ADEs) persist, leading to over 200,000 deaths annually in the European Union alone. Although CPOE and CDS systems help prevent many types of adverse drug events, many more remain undetected, unrecognized, or ill-managed. Moreover, EHRs, CPOEs, and CDS systems have introduced new errors due to the daily overflow of alerts raised, causing alert fatigue among healthcare professionals.

The first part of this thesis focused on clinical decision support systems in relation to (potential) adverse drug events. Chapter 1.1 presented the thesis problem, objective, and outline. Chapter 1.2 reviewed the variability and use of CDS systems. The following questions were investigated: What is a clinical decision support system? Why are CDS systems needed in pharmacotherapeutic healthcare? Why are results on the efficacy and successful implementation of such systems highly variable? The characteristics of such systems were studied to help understand and interpret the body of knowledge on CDS systems. The following characteristics were discussed: system function, models for giving advice, communication style, human–computer interaction, and the underlying decision-making process. These characteristics play a crucial role in determining the success of CDS system implementation. The review further explored the most widely implemented and accepted CDS systems in pharmacotherapeutic healthcare: CDS systems using decision tree models, also known as clinical rules, for decision-making and active alerts to give critiquing advice. Implementing such CDS systems has led to new challenges, such as alert fatigue, while failing to prevent frequent potential ADEs. From a model standpoint which characteristics within a decision tree model cause these problems, and how can they be solved? Triggers are the starting point in such models. For over 90% of all clinical rules, the medication order is the model’s starting point, while by far, most potential ADEs are not related to starting a drug. Therefore, other triggers should be explored to detect potential ADEs unrelated to starting a drug. The next factor studied was the circumstances influencing a decision model or advice. Such circumstances are called contextual modulators, or context, and refer to any information that could influence the decision or advice. Previous studies have demonstrated that a lack of contextualization in CDS systems is the most significant factor contributing to alert overrides. Crucial types of context influencing decisions are workflow context (user context) and clinical context (patient context). The question is which context is needed and when. The review continued by describing proven methods leading to successful clinical rule implementations, from identifying a problem to programming decisions while incorporating the context required to provide the correct advice at the appropriate time.

The second part of the thesis focused on adding context to current medication-related CDS systems to better detect potential ADEs. We investigated whether adding context to a basic CDS system could improve alerting quality for the most frequently overwritten medication alerts: drug-drug interaction (DDI) alerts (Chapter 2.1). A crossover study was performed in a clinical pharmacy setting to investigate this hypothesis. First, a basic DDI-CDS system was used in clinical practice while contextualized DDI alerts were collected in the background. Afterward, this process was reversed. Clinical utility was assessed by measuring the following parameters: positive predictive value (PPV), negative predictive value (NPV), the number of pharmacy interventions (PIs) per 1,000 medication orders (MOs), and the median time spent on DDI management per 1,000 MOs. The study demonstrated that contextualized DDI management has far greater clinical utility than basic DDI management. Clinical utility improved for all the outcome measures; PPV was 35.3% higher in the contextualized DDI management process while maintaining an NPV of 100%. In addition, the number of PIs increased from 1.6/1,000 MOs to 4.0/1,000 MOs with contextualized DDI management, suggesting a high degree of alert fatigue with basic CDS-DDI management. Furthermore, time spent on DDI management per 1,000 MOs decreased from 37.2 min per 1,000 MOs to 13.7 min per 1,000 MOs.

We also investigated whether free-text electronic hospital health record notes can be used as context to help detect ADRs (Chapter 2.2). To prevent unintended represcriptions and the risk of recurrent ADRs (reADRs), CDS systems were implemented to alert prescribers when medication is represcribed after having been previously stopped due to an ADR. Currently, however, CDS systems only function when an ADR is registered as structured information at the level of the individual patient within an ADR module linked to or part of the computerized physician order entry (CPOE) system in the electronic health record (EHR). In current clinical practice, registration is poorly performed due to time constraints, inadequate IT systems, a lack of peer support, and failure to acknowledge the importance of structurally registering ADRs. Healthcare professionals frequently describe ADRs only in clinical notes and discharge summaries, using free-text entries, which are ineffective in preventing unintended represcriptions. This study aimed to develop strategies to identify ADRs from free-text notes in electronic hospital health records. The study was performed in two stages. Stage I reviewed the EHRs of ten patients to establish strategies for identifying ADRs. Stage II reviewed the complete EHR histories of forty-five patients for ADRs and compared them to the strategies programmed into a rule-based model. ADRs were classified using MedDRA and included in the study if the Naranjo causality score was ≥1. Seriousness was assessed using the European Medicine Agency's important medical event list. Two main search strategies were identified: keywords indicating an ADR and specific prepositions followed by medication names. The 45 patient EHRs contained a median of 7.4 (range 0.01–18) years of medical history, covering over 35,000 notes. Of these 35,000 notes, 318 unique ADRs were identified, of which 63 were potentially serious; 179 (sensitivity 57%)

of these were identified by the rule. The rule falsely identified 377 ADRs (PPV 32%). However, it also identified an additional eight ADRs. We concluded that these two key strategies show promise and warrant further study.

The third part of the thesis focused on preventing potential ADRs in the monitoring phase of the medication process. We investigated the matter of medication administration via an enteral feeding tube (Chapter 3.1), a frequent cause of errors resulting in increased morbidity and cost. However, studies on interventions to prevent these errors in hospitalized patients are limited. This study aimed to investigate the effect of contextualized CDS system-assisted pharmacy intervention on the incidence of feeding tube-related medication errors (FTRMEs) in hospitalized patients. Therefore, we performed a pre-post intervention study. All patients admitted to bowel and liver disease, oncology, or neurology wards and taking oral medication via an enteral feeding tube were included for a given period. Pre-intervention patients were given care as usual. The intervention consisted of implementing a CDS system-assisted pharmacy check while applying standard operating procedures and educating personnel. An FTRME was defined as administering inappropriate medication through an enteral feeding tube. The incidence was expressed as the number of FTRMEs per medication administration. Multivariate Poisson regression calculated the incidence ratio (IR), comparing both phases. Eighty-one patients were included, 38 during pre-intervention and 43 during the intervention phase. The incidence of FTRMEs in the pre-intervention phase was 0.15 (95% confidence interval [CI] 0.07–0.23) versus 0.02 (CI 0.00–0.04) during the intervention phase, resulting in an adjusted IR of 0.13 (CI 0.10–0.18), demonstrating that the use of contextualized CDS pharmacy interventions can result in a substantial reduction in the incidence of feeding tube-related medication errors.

The medication context and pharmacist interpretation were added to alert physicians to severe hypokalemia (Chapter 3.2). Actively alerting physicians about all critical care values using telephone or electronic pop-ups can improve response. However, it can also lead to alert fatigue and frustration due to nonspecific and overdue alerts. A clinical rule built into a clinical decision support (CDS) system only generated alerts for patients with a serum potassium level (SPL) <2.9 mmol/L without a prescription for potassium supplementation. If the alert was deemed clinically relevant, a pharmacist contacted the physician. This study evaluated the impact of clinical rule-guided pharmacist intervention compared to displaying passive alerts in electronic health records for outcomes in patients who developed hypokalemia (<2.9 mmol/L) during hospitalization. A before (2007–2009) and after (2010–2017) study with a time-series design was performed. The percentage of hypokalemic patients with a subsequent prescription for potassium supplementation, time to subsequent potassium supplementation prescription, the percentage of patients who achieved normokalemia (SPL ≥3.0 mmol/L), time to achieve normokalemia, and total hospitalization duration were compared. Six hundred and ninety-three patients were

included, of whom 278 participated in the intervention phase. The percentage of patients prescribed supplementation and the time to prescription improved from 76.0% in 31.1 h to 92.0% in 11.3 h ($p < 0.01$). The time to achieve SPL ≥3.0 mmol/L improved ($p < 0.009$). However, no changes were observed in the percentage of patients who achieved normokalemia or the time to reach it: 87.5% in 65.2 h pre-intervention compared to 90.2%, ($p = 0.69$) in 64.0 h ($p = 0.71$) in the intervention group. An non-significant decrease in hospitalization duration of 8.2 days was observed: 25.4 compared to 17.2 days ($p = 0.29$). Adding further context can vastly reduce the number of active alerts and still be an effective method of improving response rates, the time to supplementation, and the time to initial improvement.

Chapter 4 places the studies we performed into a broader context. The first part of the chapter focuses on translating medical knowledge into clinical practice guidelines and, eventually, clinical decision support guidelines. While reviewing this process, recommendations were made for how this process can and should be accelerated using clinical networks, directly incorporating this knowledge into existing CDS systems and designing clinical rules to be interoperable and sharable.

The second part of the chapter focuses on CDS system outputs, predominantly alerts. How do alerts work? What is the problem with (too many) alerts? Moreover, how do humans handle many alerts? Subsequently, the leap was made toward a solution introducing context, types of context, and the use of context in CDS systems. The final part of the chapter zooms out and discusses the use of different artificial intelligence models, predominantly comparing the advantages and disadvantages of rule-based models versus machine or deep learning models.

CHAPTER 5.2

Samenvatting

SAMENVATTING

Sinds de publicatie van het rapport "To Err is Human" zijn er al duizenden miljarden euro's uitgegeven aan de implementaties van elektronische patiëntendossiers (EPD's), vaak met een geïntegreerd elektronisch voorschrijfsysteem (EVS) inclusief klinisch beslissingsondersteunend systeem. Ondanks al deze inspanningen blijven de vermijdbare schadelijke bijwerkingen voortduren. Alleen al in de Europese Unie lijdt dit jaarlijks al tot meer dan 200.000 sterfgevallen. Hoewel elektronische voorschrijfsystemen en klinische beslissingsondersteunende systemen helpen bij het voorkomen van vele soorten potentiële bijwerkingen, blijven nog vele meer nog steeds onopgemerkt, niet herkend of slecht behandeld. Ook heeft het implementeren van dergelijke systemen geleid tot signaalmoeheid. Dit betekend dat kritieke medicatiebewakingsmeldingen samen met onbelangrijke medicatiebewakingsmeldingen worden genegeerd, waardoor de patiëntveiligheid juist negatief wordt beïnvloed.

Het eerste deel van dit proefschrift richtte zich op klinische beslissingsondersteunende systemen in relatie tot (potentiële) bijwerkingen van medicijnen in de ziekenhuispraktijk. In hoofdstuk 1.1 wordt het probleem, doel en overzicht van dit proefschrift gepresenteerd. In hoofdstuk 1.2 wordt de diversiteit van klinische beslissingsondersteunende systemen besproken. De volgende vragen werden onderzocht: Wat is een klinisch beslissingsondersteunend systeem precies? Waarom zijn klinische beslissingsondersteunende systemen nodig in de klinische farmacotherapeutische zorg? Waarom zijn de resultaten over de effectiviteit en succesvolle implementatie van dergelijke systemen sterk variabel? Om de kennis die hierover beschikbaar is te kunnen interpreteren en analyseren werden eerst de belangrijkste kenmerken van dergelijke systemen besproken. De volgende kenmerken komen aan bod: systeemfunctie, modellen voor het geven van advies, communicatiestijl, mens-computer-interactie en het onderliggende besluitvormingsproces. Deze kenmerken spelen een cruciale rol bij het bepalen van het succes van de implementatie van klinische beslissingsondersteunende systemen. Dit hoofdstuk exploreerde verder de huidig meest geïmplementeerde en geaccepteerde klinische beslissingsondersteunende systemen in de farmacotherapeutische zorg: klinische beslissingsondersteunende systemen die besluitvorming ondersteunen met behulp van beslisboommodellen, ook wel bekend als klinische beslisregels welke actieve signalen genereren indien de handelingen van zorgverlener afwijken van een klinische beslisregelen (bekritiserende feedback). Het implementeren van dergelijke klinische beslissingsondersteunende systemen heeft geleid tot nieuwe uitdagingen, zoals signaalmoeheid, terwijl het nog steeds faalt om frequente potentiële bijwerkingen te voorkomen. Hoe komt dit? Bij een klinische beslisregel is er een startpunt nodig. Bij meer dan 90% van alle klinische beslisregels is de medicatieopdracht het startpunt van het model, terwijl veruit de meeste potentiële bijwerkingen helemaal niet gerelateerd zijn aan het starten van een medicijn. Daarom zouden andere startpunten

moeten worden onderzocht om potentiële bijwerkingen te detecteren die niet gerelateerd zijn aan het starten van een medicijn. De volgende factoren die werden bestudeerd, waren 'externe' omstandigheden. Dergelijke omstandigheden worden contextuele modulatoren genoemd, ofwel context, en verwijzen naar alle informatie die de beslissing of het advies zouden kunnen beïnvloeden. Eerdere studies hebben aangetoond dat een gebrek aan context in meldingen gegenereerd door klinische beslissingsondersteunende systemen de belangrijkste reden zijn voor zorgverleners om signalen te negeren (zonder te lezen weg te klikken ofwel door te enteren). Zorgverleners noemen als belangrijkste reden hiervoor het ontbreken van workflow-context ofwel gebruikerscontext en klinische context ofwel patiëntcontext. Het hoofdstuk gaat verder met het beschrijven van bewezen methoden voor succesvolle implementaties van klinische beslisregels, van het identificeren van een probleem tot het programmeren van beslissingen waarbij de vereiste context wordt geïntegreerd om op het juiste moment het juiste advies te geven.

Het tweede deel van het proefschrift richtte zich op het toevoegen van context aan huidige klinische beslissingsondersteunende systemen die betrekking hebben op medicatie om potentiële bijwerkingen beter op te kunnen sporen. Hoofdstuk 2.1 bestudeerd de meest genegeerde medicatiebewakingssignalen in de klinische praktijk: geneesmiddel-geneesmiddelinteracties. Met de huidige klinische beslissingsondersteunende systemen wordt altijd een signaal gegeneerd als geneesmiddel A wordt gecombineerd met interacterend geneesmiddel B. Er werd onderzocht of het toevoegen van context, zowel gebruikerscontext als klinische context, de bruikbaarheid van de interactiesignalen kon verbeteren. Hiervoor werd een cross-over studie uitgevoerd in een ziekenhuisapotheekomgeving. Eerst werd de contextloze variant van het klinische beslissingsondersteunend systeem in de klinische praktijk gebruikt voor behandeling van geneesmiddel-geneesmiddelinteracties, . gelijktijdig werden de van context voorziene interactiesignalen op de achtergrond verzameld. Daarna werd dit proces omgekeerd. De klinische bruikbaarheid van de twee varianten werd beoordeeld door de volgende parameters te meten: positieve voorspellende waarde (PVW), negatieve voorspellende waarde (NVW), het aantal apotheekinterventies per 1.000 medicatieopdrachten en de mediane tijd besteed aan de behandeling van geneesmiddel-geneesmiddelinteracties per 1.000 medicatieopdrachten. De studie toonde aan dat het klinische beslissingsondersteunende systeem welke de geneesmiddel-geneesmiddel interacties van context voorzag en waar nodig ook verborg, een veel grotere klinische bruikbaarheid had dan de contextloze klinische beslissingsondersteuning. De klinische bruikbaarheid verbeterde voor alle uitkomstmaten; PVW was 35,3% hoger in het van context voorziene geneesmiddel-geneesmiddel interactie beheer proces, terwijl een NVW van 100% werd behouden. Bovendien nam het aantal apotheekinterventies toe van 1,6/1.000 medicatieopdrachten naar 4,0/1.000 medicatieopdrachten met de van context voorziene klinische beslissingsondersteuning. Dit suggereert een hoge mate van signaalmoeheid met

de huidige gebruikte klinische beslissingsondersteuning. Bovendien nam de tijd die besteed werd aan geneesmiddel-geneesmiddelinteracties per 1.000 medicatieopdrachten af van 37,2 minuten naar 13,7 minuten per 1.000 medicatieopdrachten.

In hoofdstuk 2.2 werd onderzocht of de vrije tekst uit het elektronisch patiëntendossier kan worden gebruikt om potentieel geregistreerde bijwerkingen te detecteren. Een aanzienlijk deel (13-50%) van alle potentieel vermijdbare ziekenhuisopnames door bijwerkingen is toe te schrijven aan het onbedoeld opnieuw voorschrijven van medicatie waarvan al bekend is dat de patient hier eerder bijwerkingen op heeft ontwikkeld. Bijvoorbeeld het opnieuw voorschrijven van een geneesmiddel waar de patient eerder een allergische reactie op heeft ontwikkeld. Een van de eerste vormen van klinisch farmaceutische beslissingsondersteuning die werden geïmplementeerd waren systemen die voorschrijvers konden waarschuwen wanneer deze iets voorschreven waar de patient eerder bijwerkingen van had gehad. Deze klinisch beslissingsondersteuning functioneert echter alleen wanneer deze eerdere bijwerkingen in de hiervoor bestemde bijwerkingenmodule van het EVS of EPD zijn ingevoerd. In de huidige klinische praktijk wordt de registratie van een bijwerking in een dergelijke module echter niet of slecht uitgevoerd, vanwege tijdgebrek, ontoereikende ICT-systemen, een gebrek aan groepsdruk/ondersteuning en het niet erkennen van het belang van gestructureerde vastleggen hiervan. Zorgprofessionals in ziekenhuizen leggen bijwerkingen vaak alleen vast in de naslag (klinische notities) en ontslagbrieven, met behulp van vrije tekstnotities. Deze manier van vastleggen is echter niet effectief gebleken om onbedoeld opnieuw voorschrijven van medicatie te voorkomen.

Het onderzoek had als doel strategieën te ontwikkelen om bijwerkingen te identificeren uit de naslag van een ziekenhuis EPD. Het onderzoek werd in twee fasen uitgevoerd. In fase I werden de elektronische patiëntendossiers van tien patiënten gelezen door twee zorgverleners om strategieën voor het identificeren van bijwerkingen uit vrije tekst vast te stellen. Deze strategieën voor identificatie werden vervolgens geprogrammeerd in het klinisch beslissingsondersteunende systeem. In fase II werd deze geprogrammeerde klinische beslisregel ingezet om de elektronische patiëntendossiers van vijfenveertig patiënten op bijwerkingen te screenen. Dit werd vergeleken met het handmatig screenen van deze dossiers. Bijwerkingen werden geclassificeerd met behulp van Medical Dictionary for Regulatory Activities (MedDRA) codes en geïncludeerd in de studie bij een Naranjo-causaliteitsscore ≥1. Ernst van de bijwerkingen werd beoordeeld met behulp van de lijst van belangrijke medische gebeurtenissen van het Europees Geneesmiddelenbureau (EMA). Twee belangrijke zoekstrategieën werden geïdentificeerd n.a.v. fase I + II: trefwoorden die wijzen op bijwerkingen en specifieke voorzetsels gevolgd door medicijnnamen. De geïncludeerde elektronische patiëntendossiers hadden een mediane geschiedenis van 7,4 (bereik 0,01-18) jaar aan medische informatie, met meer dan 35.000 vrije tekstnotities. Binnen deze 35.000 notities werden 318 unieke bijwerkingen geïdentificeerd, waarvan er 63 mogelijk ernstig waren; 179 (sensitiviteit 57%) hiervan werden geïdentificeerd door de klinische beslisregel.

De regel identificeerde 377 bijwerkingen ten onrechte (PVW 32%). De klinische beslisregel identificeerde echter ook acht aanvullende bijwerkingen. We concludeerden dat de twee belangrijkste strategieën die geïdentificeerd zijn veelbelovend zijn en verder onderzoek rechtvaardigen.

Het derde deel van dit proefschrift richtte zich op het voorkomen van mogelijke bijwerkingen in de monitoringsfase van het medicatieproces. Het probleem van toediening via een voedingssonde werd onderzocht (hoofdstuk 3.1), een veelvoorkomende oorzaak van medicatiefouten die leiden tot verhoogde morbiditeit en kosten. Er zijn weinig studies naar interventies om deze fouten bij in het ziekenhuis opgenomen patiënten te voorkomen. Deze studie had als doel om het effect van een apotheekinterventie ondersteunend door een context bewust klinische beslissingsondersteunend systeem op de incidentie van voedingssonde gerelateerde medicatiefouten bij gehospitaliseerde patiënten te onderzoeken. Om dit te onderzoeken werd een prospectieve pre-post interventiestudie uitgevoerd. Alle patiënten opgenomen op de afdelingen voor maag, darm- en leverziekten, oncologie of neurologie die orale medicatie via een voedingssonde kregen gedurende een bepaalde periode werden geïncludeerd. Voor de interventie kregen pre-interventiepatiënten de gebruikelijke zorg. De interventie bestond uit het implementeren van een door een beslissingsondersteunende systeem ondersteunde apotheekinterventie i.c.m. implementatie van standaardwerkprocedures en het aanvullend opleiden van personeel (apothekersassistentes en verpleegkundigen). Een voedingssonde gerelateerde medicatiefout werd gedefinieerd als het toedienen van ongeschikte medicatie via een voedingssonde. De incidentie werd uitgedrukt als het aantal voedingssonde gerelateerde medicatiefouten per medicijntoediening. De incidentieratio (IR) werd berekend middels multivariate Poisson-regressie waarna beide fasen werden vergeleken. Een totaal van 81 patiënten werd geïncludeerd, 38 in de pre-interventiefase en 43 in de interventiefase. De incidentie van voedingssonde gerelateerde medicatiefouten in de pre-interventiefase was 0,15 (95% betrouwbaarheidsinterval [BI] 0,07-0,23) versus 0,02 (BI 0,00-0,04) tijdens de interventiefase (85% reductie), wat resulteerde in een aangepaste IR van 0,13 (BI 0,10-0,18), wat aantoont dat het gebruik van op de context gebaseerde beslissingsondersteunende systeem apotheekinterventies kan resulteren in een aanzienlijke vermindering van de incidentie van voedingssonde gerelateerde medicatiefouten.

In hoofdstuk 3.2 werd aan de standaard passieve signalen over hypokaliëmieën die voorschrijvers in het ziekenhuis ontvangen, medicatiecontext en interpretatie van een apotheker toegevoegd. Uit voorgaande onderzoeken is gebleken dat de respons op ernstige hypokaliëmieën die alleen passief in het elektronisch patiënten dossier werden gemeld, ondermaats is. Waarschuwen van voorschrijvers middels telefonische of actieve elektronische waarschuwingen kan de respons significant verbeteren, maar leidt weer tot signaalmoeheid en frustratie door de toename van niet-specifieke en vaak onnodige waarschuwingen.

Een klinische beslisregel, ingebouwd in een klinisch beslissingsondersteunend systeem genereerde actieve signalen voor patiënten met een serumkaliumspiegel (SPS) <2,9 mmol/L zonder een voorschrift voor kaliumsuppletie. Indien hierbij een klinisch relevant signaal naar voren kwam, nam een apotheker contact op met de arts. De studie evalueerde de impact van deze door klinische beslisregel ondersteunde apothekersinterventie, in vergelijking met passieve waarschuwingen in het elektronische patiëntendossier voor patiënten die tijdens hun ziekenhuisopname hypokaliëmie (SPS <2,9 mmol/L) ontwikkelden. Er werd een voor- (2007-2009) en na-onderzoek (2010-2017) uitgevoerd met tijdsreeksanalyse. De eindpunten van deze studie waren het percentage hypokaliëmische patiënten waarbij een medicatie opdracht voor kaliumsuppletie werd voorgeschreven, de tijd tot het voorschrijven van deze kaliumsuppletie, het percentage patiënten dat normokaliëmie (SPS ≥3,0 mmol/L) bereikte, de tijd tot het bereiken van normokaliëmie en de totale duur van ziekenhuisopname. In totaal werden 693 patiënten opgenomen in de studie, waarvan er 278 werden geïncludeerd in de interventiefase. Het percentage patiënten dat kaliumsuppletie kreeg voorgeschreven en de tijd tot het voorschrijven hiervan verbeterden van 76,0% in 31,1 uur naar 92,0% in 11,3 uur (p <0,01). Ook de tijd tot het bereiken van milde hypokaliëmie (SPS ≥3,0 mmol/L) verbeterde (p<0.009). Er werden echter geen veranderingen waargenomen in het percentage patiënten dat normokaliëmie bereikte of de tijd om dit te bereiken: 87,5% in 65,2 uur vóór de interventie in vergelijking met 90,2%, (p = 0,69) in 64,0 uur (p = 0,71) in de interventiegroep. Wel werd er een niet-significante afname van de duur van de ziekenhuisopname waargenomen met 8,2 dagen: van 25,4 naar 17,2 dagen (p = 0,29). Het toevoegen van verdere context kan het aantal actieve waarschuwingen aanzienlijk verminderen en tegelijkertijd een effectieve methode zijn om responspercentages, de tijd tot kaliumsuppletie en de tijd tot initiële verbetering te verbeteren.

De algemene discussie (hoofdstuk 4) plaatst de studies die zijn uitgevoerd in een bredere context. Het eerste deel van het hoofdstuk richt zich op het vertalen van medische kennis naar klinische praktijkrichtlijnen en uiteindelijk klinische beslissingsondersteunende richtlijnen. Tijdens het bekijken van dit proces worden aanbevelingen gedaan over hoe dit proces kan en zou moeten worden versneld met behulp van klinische netwerken, door deze kennis direct in bestaande klinische beslissingsondersteunende systemen te incorporeren en klinische regels zo te ontwerpen dat ze interoperabel en deelbaar zijn.

Het tweede deel van het hoofdstuk richt zich op de uitvoer van klinische beslissings-ondersteunend systemen, voornamelijk meldingen. Hoe werken meldingen? Wat is het probleem met (te veel) meldingen? Bovendien, hoe gaan mensen om met veel meldingen? Vervolgens wordt de sprong gemaakt naar een oplossing voor dit probleem het gebruik van context. Het laatste deel van het hoofdstuk zoomt nog verder uit en bespreekt het gebruik van verschillende vormen van kunstmatige intelligentie-modellen. Voornamelijk de vergelijking tussen de op regels gebaseerde modellen versus machinaal- of diep-lerende modellen.

CHAPTER 5.3

Dankwoord

"It does not matter how slowly you go as long as you do not stop."
Confucius

DANKWOORD

Deze ontdekkingstocht heeft niet het meest standaard karakter gehad. Maar dat zal elke promovendus mogelijk wel zo beleven. Het is je eigen unieke ontdekkingstocht met hoge pieken en diepere dalen. Met stilstand en vooruitgang, met uitzichtloosheid en enthousiasme.

Allereerst wil ik iedereen bedanken die een bijdrage heeft geleverd aan dit proefschrift: alle coauteurs, (ziekenhuis)apothekers (in opleiding), studenten farmacie en geneeskunde, artsen, apothekersassistenten en verpleegkundigen en vele meer die mogelijk ben vergeten in dit dankwoord. Maar vanzelfsprekend wil ik me tot een aantal mensen in het bijzonder richten.

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Beste René, “zullen we even een luchtje scheppen?” deze onvergetelijke woorden kondigden spontane overleggen aan waarin we onze gedachten de vrije loop konden laten en nieuwe ideeën konden ontwikkelen. Je was op dagelijkse basis betrokken bij alle onderzoeken, vraagstellingen en strubbelingen, je dacht over alle aspecten mee, van de techniek en redeneringen tot de bewoording in management samenvattingen richting Santeon bestuur. Ik wil je bedanken voor je vriendschap, betrokkenheid en vertrouwen. Ook zonder jou was dit proefschrift er niet geweest, maar was ik ook niet de ziekenhuisapotheker geweest die ik nu ben. Naast alle direct onderzoeksgerelateerde vaardigheden heb ik zo ontzettend veel

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Dan wil ik graag mijn paranimfen in het bijzonder bedanken.

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Alle onderzoeken hebben plaatsgevonden in het Catharina Ziekenhuis Eindhoven. Ik wil alle apothekersassistenten en (ziekenhuis) apothekers (i.o.), farmaciestudenten, geneeskundestudenten, artsen, verpleegkundigen, HCI, ICMT en O&O medewerkers ontzettend bedanken voor hun hulp. Een aantal mensen wil ik in het bijzonder bedanken voor hun bijdrage.

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Beste Carolien, jouw proefschrift was een inspiratiebron. Het liet me zien hoe ontzettend onderbelicht bijwerkingen eigenlijk zijn en dan ook met name bijwerkingen waarvan de patient ze zelf al een keer ervaren heeft. Het heeft mijn interesse als ziekenhuisapotheker maar ook mijn onderzoek een hele andere kant op geduwd welke ik eerder niet voorzien had. Daarnaast wil ik je bedanken voor de goede gesprekken die we hebben gehad over wat het betekende om promovendus te zijn en dat dit met vallen en opstaan alsnog goed kan komen, dank je wel.

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Beste Naomi, jouw werk en visie is ook een inspiratiebron geworden voor dit proefschrift. Het heeft ervoor gezorgd dat ik registratie en detecteren van bijwerkingen ook in een breder perspectief kon plaatsten. Goede registratie bij een patient hoeft niet alleen leiden tot het voorkomen van bijwerkingen bij die patient maar ook bij zovele meer. Daarnaast bedankt voor al het monniken werk wat je hebt verricht als coauteur met de causaliteitsbeoordeling van alle bijwerkingen.

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CHAPTER 5.4

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CHAPTER 5.5

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CHAPTER 5.6

List of abbreviations

LIST OF ABBREVIATIONS AS PRESENTED IN THIS THESIS

All abbreviations are listed as singular

AE: Adverse event
ADE: Adverse drug event
ADR: Adverse drug reaction
AI: Artificial intelligence
ANN: Artificial neural network
AMIA: American Medical Informatics Association
ATC: Anatomical therapeutic chemical
CDS: Clinical decision support
CPOE: Computerized physician order entry
CR: Clinical rule
CI: Confidence interval
CIG: Computer-interpretable guidelines
CRISP: Clinical rules in Santeon project
CYP: Cytochrome P450
CZE: Catharina Hospital Eindhoven
DDI: Drug-drug interaction
EPOC: Effective Practice and Organization of Care Group
EBM: Evidence based medicine
EHR: Electronic health record
EMA: European medicine agency
FP: False positive
FN: False negative
FT: Free-text (Chapter 2.2)
FT: Enteral feeding tube (Chapter 3.1)
FTE: Full-term equivalent
FTRME: Feeding tube-related medication error
FOLFOX: Combination therapy of fluorouracil and oxaliplatin
GLIF: Guideline interchange format
HCTZ: Hydrochlorothiazide
ICD-10: International Statistical Classification of Diseases and Related Health Problems (10th ed.)
IR: Incidence ratio
ICU: Intensive care unit

KNMP: Dutch Royal Society of Pharmacists – Koninkelijke Nederlandse maatschapij ter bevoordering van der Pharmacie
LIS: Laboratory information system
MO: Medication order
ME: Medication error
MEDRA: Medical Dictionary for Regulatory Activities
NPV: Negative predictive value
NSAID: Nonsteroidal anti-inflammatory drug
NVZA: Dutch Association of Hospital Pharmacists – Nederlandse vereninging voor ziekenhuisapothekers
PKPD: Pharmacokinetic and dynamic model
PIS: Pharmacy information system
PDCA: Plan-Do-Check-Act
PPV: Prospective predictive value
PPI: Proton-pump inhibitor
RAAS: Renin-angiotensin-aldosterone system
RAASi: Renin-angiotensin-aldosterone system inhibitor
reADR: Recurrent adverse drug event
SmPC: Summary of product characteristics
SMS: Short message service
SPL: Serum potassium level
TP: True positive
URD: User requirements documentation
URS: User requirements specification
WHO: World Health Organization

CHAPTER 5.7

About the author

"*Be the change that you wish to see in the world.*"
Mahatma Gandhi

ABOUT THE AUTHOR

Arthur Wasylewicz was born 16th September 1987 in Wageningen were he also grew up. He discovered his interest in chemistry and biology at his high school Pantarijn and decided to study Pharmacy at Utrecht University. Early in his student years, he chose to become a hospital pharmacist. During his master's research internship in Eindhoven, he realized he had the skills and deep interest to combine technological solutions to solve problems in pharmaceutical healthcare. In August 2012 he graduated as a pharmacist and continued to work in Eindhoven. A year later, he began training to become a hospital pharmacist. During training, he continued developing, implementing, and studying clinical decision support solutions to help solve various problems in monitoring the efficacy of drug therapy and prevent adverse drug events.

He transferred to St. Antonius hospital in Nieuwegein and Utrecht for his exchange year. A fatal medical tragedy due to the re-administration of a drug in a patient compelled him to deepen his medical knowledge of allergic reactions and other adverse drug reactions during his final year as a trainee hospital pharmacist at the department of allergology at UMC Utrecht.

In 2019, he attained the position of hospital pharmacist. After remaining in Eindhoven for another year, he changed course and became the first seconded hospital pharmacist at Lead Healthcare (previously PharmaLead). In this role, he helped numerous hospital pharmacies in the Netherlands with IT and clinical decision support-related projects. Parallel to this and continuing his research in Eindhoven, he became involved in multiple national working parties to improve the detection, registration, and exchange of adverse drug reactions in patients in the Netherlands. He also became a member of the working parties to judge and refine drug-drug interactions and double medication alerts for the Dutch Royal Society of Pharmacists (KNMP). Moreover, he is a member of the commission for information technology and healthcare of the Dutch Association of Hospital Pharmacists (NVZA), focusing on the use of artificial intelligence.

Arthur lives in 's-Hertogenbosch with his high school sweetheart, Celestine, and their daughter Madelynn (11-2021).

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