# DRUG-RELATED PROBLEMS
## Risk Factors and the Role of Clinical Pharmacists

Rianne Zaal

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Risk Factors and the Role of Clinical Pharmacists

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Risicofactoren en de rol van apothekers

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TABLE OF CONTENTS

# 1

# General Introduction

Pharmacotherapy is an essential aspect of medical treatments for curing or ameliorating diseases, relieving symptoms or preventing future complications. To achieve an optimal outcome one should ensure that the right drug is prescribed and administered to the right patient for the right reason in the right dosage and form, via the right route, at the right time with the right documentation and the right monitoring.[1] Unfortunately drug-related problems, defined as circumstances during drug treatment that actually or potentially interfere with the achievement of the optimal outcome do occur.[2]

## DRUG-RELATED PROBLEMS

Drug-related problems include medication errors and adverse drug events. Definitions of these terms and their relationship are presented in figure 1.

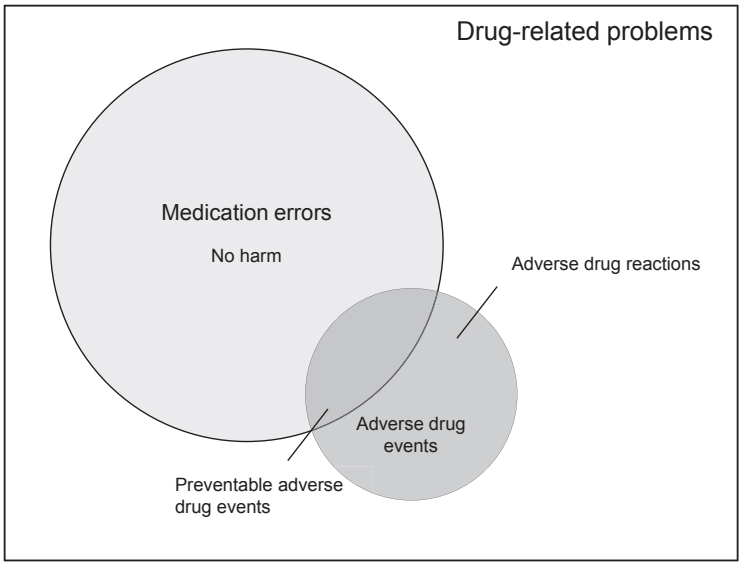


**Figure 1:** Drug-related problems and their relationships

| | |
|---|---|
| Drug-related problems | Circumstances during drug treatment that actually or potentially interfere with the achievement of an optimal outcome.[2] |
| Medication errors | Any error in the process of prescribing, transcribing, dispensing or administering a drug, whether there are adverse consequences or not.[4] |
| Adverse drug events | An injury resulting from medical intervention related to a drug.[13] |
| Preventable adverse drug events | An adverse drug event resulting from a medication error.[85] |
| Adverse drug reactions | A noxious and unintended response which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.[9] |

The publication of the report "To err is human" in 1999 showed that medication errors account for an increase in hospital costs of about $2 billion and over 7,000 deaths annually in the United States of America at that time.[3] Since then, health care professionals increased their efforts to improve medication safety and studied the occurrence of drug-related problems and their risk factors intensively, in particular in hospitalized patients.

## Medication errors and preventable adverse drug events

Medication errors are defined as any error in the process of prescribing, transcribing, dispensing or administering a drug, whether there are adverse consequences or not.[4] Errors occur when intended actions fail to proceed as intended (i.e. skill-based slips or memory-based lapses) or when the wrong plan is used to achieve the desired consequences (i.e. mistakes).[5]

A review on drug-related problems, published in 2007, indicated that about 6% of all medication orders prescribed to hospitalized patients, result in an error and most of these errors are made during prescribing and administering a drug.[6] However, the prevalence varies highly, depending on the definition, detection method and setting.[2, 6]

It has been estimated that at most 10% of all medication errors result in patient harm, affecting 1% to 15% of hospitalized patients.[6-8] This patient harm can vary from mild temporary discomfort to death. These harmful events caused by medication errors are referred to as preventable adverse drug events. For example, when penicillin is prescribed by mistake to a patient with a documented allergy for this drug, and the patient develops an anaphylactic reaction, this reaction could have been prevented by an electronic alert at the time of prescribing of the contra-indicated drug to this patient. Common other examples of medication errors that may result in preventable adverse drug events include overdoses of opiates leading to sedation or respiratory depression and lack of monitoring of anticoagulants leading to hemorrhage.[7]

## Adverse drug reactions

However, even without the existence of medication errors, the intrinsic toxicity of drugs can lead to patient harm. If, for example, the same penicillin is prescribed to a patient who has been treated before with this drug without any signs of allergy, the patient can develop an allergic reaction. Such noxious and unintended responses to drugs occurring at doses normally used are called adverse drug reactions[9] and occur in about 7% to11% of hospitalized patients.[2, 10]

## Adverse drug events

Together, preventable adverse drug events and adverse drug reactions are called adverse drug events, which affect about 6% of hospitalized patients.[11]

It has been estimated in several studies that one quarter to more than half of the adverse drug events are related to medication errors.[6, 7, 12-15] In primary care settings, where the

median prevalence of adverse drug events is 20%, about 16% of the events are thought to be preventable.[16]

In the Netherlands adverse drug events in hospitalized patients result in an excess length of stay of about 6 days and additional costs of more than €2500 per event.[17] In addition, approximately 5% of acute hospital admissions in the Netherlands can be attributed to adverse drug events, of which about 40% are judged to be potentially preventable, resembling the rates reported in the United States of America and Australia.[15, 18]

In comparison to medication errors, adverse drug events are more difficult to detect and assess. First, adverse drug events occur less frequently than medication errors. Second, a causality assessment using an algorithm is required to evaluate the likelihood that a drug was the causative agent of an observed event.[9] Since this assessment can vary according to the professional background of the assessors, a consensus method, in which both pharmacists and physicians are involved, is recommended.[19] Due to these difficulties medication errors are more often used as outcome to measure the effect of medication safety initiatives than (preventable) adverse drug events, assuming that a reduction of medication errors will subsequently lead to a reduction of adverse drug events. These safety initiatives are mainly targeted to identified risk factors for medication errors. However, risk factors for adverse drug events may (partly) differ from risk factors for medication errors, which would require different safety initiatives. Risk factors for the different types of drug-related problems have not been compared directly up to now.

## RISK FACTORS FOR DRUG-RELATED PROBLEMS

Knowledge on the origin of drug-related problems is a first step in reducing these problems. Therefore, risk factors for drug-related problems have been intensively studied. An overview of identified risk factors for drug-related problems is presented in table 1. In general, characteristics of the organization, the patient and the drug have all three been associated with the occurrence of drug-related problems.

Characteristics of the organization, including pharmacy services, have been associated with the occurrence of medication errors in particular.[6, 20-22] The association of such organizational characteristics with (preventable) adverse drug events has not been assessed, except for ward type and lack of information about drugs or the patient.[4, 7] On the other hand, patient characteristics, such as age[6, 15, 23, 24] and the number of drugs used,[6, 18, 24] have been mostly related with adverse drug events, reflecting a patient's vulnerability to harm. Renal failure[6, 18, 25] and liver failure[23, 25] as comorbidity, requiring dose modifications or switching of contra-indicated drugs, have been associated with both medication errors and adverse drug events.

**Table 1:** Risk factors for medication errors, preventable adverse drug events and adverse drug events (ADE)

| Risk factor | Medication error | Preventable ADE | ADE |
|---|---|---|---|
| Organizational characteristics | | | |
| Ward | | ✓ [11,26] | ✓ [6,11,23,84] |
| Documentation and information | | | |
| Errors in patient charts or nurses' documentation | ✓ [6] | | |
| Lack of information about drugs or patients | ✓ [6] | ✓ [7,22] | |
| Knowledge and skills of health care professionals | | | |
| Insufficient pharmacological knowledge | ✓ [6] | | |
| Insufficient training | ✓ [20] | | |
| Surgical specialists (versus medical specialists) | ✓ [21] | | |
| Residents (versus specialists) | ✓ [21] | | |
| Pharmacy services | | | |
| Inadequate pharmacy services | ✓ [6] | | |
| Lack of standardization of the medication process | ✓ [6] | | |
| Lack of clinical pharmacists | ✓ [6] | | |
| Workload | ✓ [6,20] | | |
| Communication within a team | ✓ [20,22] | | |
| Patient characteristics | | | |
| Female gender | | | ✓ [6] |
| Age | | | ✓ [6,15,23,24] |
| Weight | | | ✓ [23] |
| Increased length of stay | | ✓ [11] | ✓ [6,11] |
| Comorbidity | | | |
| Renal failure | ✓ [25] | | ✓ [6,18] |
| Liver disease | ✓ [25] | | ✓ [23] |
| Impaired cognition | | | ✓ [18] |
| Enteral feeding tube | ✓ [21] | | |
| Thrombocytopenia | | ✓ [26] | |
| Number of comorbid conditions | | ✓ [11] | ✓ [11,18,23, 84] |
| Number of drugs and polypharmacy (≥5 drugs) | | ✓ [11] | ✓ [6,11,18,24,84] |
| Dependent living situation | | | ✓ [18] |
| Drug characteristics | | | |
| Pharmacotherapeutic group | | | |
| Drugs for gastrointestinal tract | ✓ [21] | | ✓ [6,21] |
| Anti-coagulants | ✓ [6] | ✓ [15,7] | ✓ [6,84] |
| Cardiovascular drugs | ✓ [6] | ✓ [15,7, 26] | ✓ [6,26] |
| Anti-infective agents | ✓ [6] | ✓ [7,15,17] | ✓ [17,24] |
| Antineoplastic agents | ✓ [6] | ✓ [15] | ✓ [17] |
| Drugs acting on the nervous system | ✓ [21] | ✓ [7,26] | ✓ [6,24] |
| Pharmaceutical dosage form | ✓ [6,21] | | ✓ [23] |
| Parenteral preparations | | | ✓ [23] |
| Inhalation, eye preparations, rectal preparations | ✓ [21] | | |
| Atypical dosage frequency | ✓ [25] | | |
| Continuation of pre-admission treatment | ✓ [21] | | |
| Hospital-initiated treatment | | | ✓ [24] |
| Weight-based dose calculation | ✓ [6] | | |

✓ = Identified as risk factor. Abbreviations: ADE, adverse drug event.

The pharmacotherapeutic group of the used drug seems to be the most important risk factor of the drug itself. Several drug classes, including anti-infective agents, drugs acting on the central nervous system, antineoplastic agents and anticoagulants have been related to medication errors and (preventable) adverse drug events, reflecting respectively the extrinsic and the intrinsic toxicity of these drugs.[6, 7, 15, 17, 21, 24, 26]

### Individuals with an intellectual disability: a population potentially at risk

The aforementioned risk factors are mostly addressed in hospitalized patients. Because a number of these risk factors, as described below, are pertinent in individuals with an intellectual disability in primary health care settings, this population may be especially at risk for drug-related problems.

First, they often suffer from multiple chronic morbid conditions requiring pharmacotherapy, including somatic diseases such as gastro-esophageal reflux disease,[27] epilepsy,[28] and constipation[29] as well as mental conditions, such as behavioral problems,[30] anxiety[31] and depression.[32] As a result, polypharmacy, defined as the concomitant use of five or more drugs, which has been identified as a risk factor for adverse drug events in the general population,[18] occurs in up to 60% of the individuals with an intellectual disability.

Second, the life expectancy of adults with an intellectual disability is increasing and age-related frailty seems to start at a younger age than in the general population,[33] possibly making them susceptible to inappropriate prescribing and adverse drug events.

Third, drugs acting on the central nervous system, associated with drug-related problems in the general population,[6, 7, 21, 24, 26], are often prescribed to individuals with an intellectual disability for behavioral problems,[30] notwithstanding limited evidence for this indication.[34-36]

Fourth, atypical symptoms of diseases and patients' inability to communicate about disease, complicate diagnosing, prescribing and evaluating pharmacotherapy,[37, 38] possibly leading to drug-related problems including undertreatment,[39] overtreatment[40] and disproportionate continuation of pharmacotherapy without a clear indication.[30]

Finally, living in a residential care setting and impaired cognition, both known to be associated with adverse drug events requiring hospitalization in the general population,[18] are pertinent in individuals with an intellectual disability.

Despite the presence of these risk factors, the prevalence of drug-related problems in individuals with an intellectual disability is largely unknown.

## INTERVENTIONS TO REDUCE DRUG-RELATED PROBLEMS

Although risk factors related to patient characteristics or their pharmacotherapy have been identified, risk stratification approaches to identify patients at risks are disputed to be pro-

ductive.[26] Therefore, interventions to reduce drug-related problems are mainly focused on improvements at the organizational level, including the design of the medication process and clinical pharmacy services. One critical element of a safe organization is a blame-free error reporting system, used to monitor error rates, learn from experiences and to identify risk factors for errors and measures to diminish them.[3] To increase the dissemination of knowledge obtained by these reporting systems, nationwide reporting systems have been developed in several countries.[41]

Besides, optimization of the pharmaceutical care process, such as a closed-loop system combining computerized physician order entry with barcode assisted dispensing and administering, could reduce the occurrence of drug-related problems. [42] Since this thesis focuses primarily on prescribing errors, computerized order entry will be discussed in some more detail.

### Computerized physician order entry and clinical decision support systems (CPOE/CDSS)

Computerized physician order entry in combination with clinical decision support systems, alerting physicians on potential drug-related problems during prescribing, has been shown to reduce the frequency of medication errors compared to handwritten prescribing. CPOE in combination with basic CDSS used currently in the Netherlands, providing support on dosing, drug-drug interactions, duplicate therapy and allergies, is less effective in reducing therapeutic prescribing errors, which are most strongly associated with preventable adverse drug events.[43] This probably explains why the effect of CPOE on the reduction of preventable adverse drug events is less clear.[44]

In order to reduce pharmacotherapeutic errors and preventable adverse drug events, more advanced clinical decision support, combining medication data with biochemical results and patient history in so-called clinical rules, is being developed. In addition, these clinical rules can facilitate the early detection of adverse drug reactions.

Clinical rules are partly derived from electronic trigger tools, developed in the past to monitor adverse drug events.[45-47] Examples of such rules include dose adjustments for patients with renal failure, requirement of additional drug therapy to prevent adverse drug reactions and abnormal biochemical values indicating toxicity.[45-49] A defined validation process of these rules can result in an increase in the sensitivity and the specificity of the alerts,[50] preventing alert fatigue, which is another disadvantage of basic CDSS.[51]

### Active participation of a clinical pharmacist

Another strategy to reduce drug-related problems is to integrate clinical pharmacists in the medical team on the ward. Because clinical pharmacists can combine current diagnoses, laboratory values, medical history, and prescribing guidelines with the actual pharmacotherapy of a patient they are able to reduce drug-related problems. Indeed, previous

studies have shown that participation of clinical pharmacists in the medical team can reduce prescribing errors, adverse drug events, length of stay and costs.[52, 53] However, the contribution of a clinical pharmacist in addition to CPOE/CDSS has not been well established. Besides, limited personnel resources may hamper participation of clinical pharmacists on all wards on a daily basis, necessitating selection of patients at risk for drug-related problems using clinical rules.[54]

### Medication review

Previous studies have shown that medication review, defined as a systematic assessment of an individual's pharmacotherapy that aims to evaluate and optimize medication,[55] performed by the physician and pharmacist, together with the patient, can reduce the number of drug-related problems, in particular in older patients with polypharmacy in the general population.[55-59] Recently, a systematic tool to reduce inappropriate prescribing has been developed in the Netherlands for older patients with polypharmacy to facilitate medication reviews in this specific population.[60] In this tool the Screening Tool to Alert doctors to Right Treatment (START) and the Screening Tool of Older Peoples' Prescriptions (STOPP) are included to ease the detection of drug-related problems.[61, 62] In hospitalized patients, these START/STOPP criteria significantly reduced drug-related problems, which sustained during follow up for six months after discharge.[63]

Although a multidisciplinary annual medication review is demanded by the Dutch Healthcare Inspectorate in care organizations for individuals with an intellectual disability, studies on the effect of medication review in this population are scarce. Recently, a Dutch study showed that medication review reveals drug-related problems in 80% of individuals with an intellectual disability using at least one psychotropic drug.[40]

In general, evidence for the contribution of pharmacists to patient care in this population is surprisingly scarce. O'Dwyer et al. reviewed all studies on pharmacists' contributions to the care for individuals with an intellectual disability published between 1994 and 2014.[64] They were able to include only eight studies performed in this period. The results of these studies point in the same direction, namely that collaboration between pharmacists and healthcare providers, caregivers and patients with an intellectual disability can improve patient care. Effective improvements include a reduction in administration errors in patients with an enteral feeding tube by education of caregivers, reduction of prescribing rates of psychotropic drugs by consulting service (including medication review), increasing patients knowledge on medication use by pharmacist counselling, and improvements in drug handling in organizations.[64]

## ACCEPTANCE OF PHARMACISTS' INTERVENTIONS

The organizational interventions to reduce drug-related problems, all result in the detection of potential drug-related problems in individual patients. For relevant problems that actually require a change in pharmacotherapy or additional monitoring, the clinical pharmacist will contact the responsible physician (on the ward, by telephone or electronically) to propose an intervention for the individual patient to resolve the problem. To actually reduce drug-related problems, physicians need to implement recommendations that are clinically relevant for the patient. The reported acceptance rate of pharmacists' interventions varies between 52% and 98%, depending on setting, the method of detecting drug-related problems and the means of communicating the interventions.[65-76] The type of the underlying drug-related problem, the pharmacotherapeutic group of the drug involved, the type of interventions and the medical specialty of the ward have also been associated with the acceptance rate.[67, 72, 77, 78] Most of the interventions in these studies were proposed by pharmacists that were integrated in the medical team on the ward, whereas in daily routine a substantial part of the interventions are proposed from the central pharmacy, at least in the Netherlands and surrounding countries in continental Europe. In order to improve pharmacy services and further decrease drug-related problems, detailed knowledge on the acceptance rate of interventions from these central pharmacy services and understanding of the factors that influence the acceptance rate and physicians' reasons for non-acceptance is essential.

Summarizing, drug-related problems occur frequently in hospitalized patients and numerous risk factors have been identified. However, an effective risk stratification method to identify patients at risk has not yet been developed.[26] Besides, the studied interventions to reduce drug-related problems focus mainly on one intervention, whereas multi strategy approaches, combining CPOE/CDSS, clinical rules and active participation of clinical pharmacists, are usually operated in synergy in clinical practice.

Individuals with an intellectual disability may be especially at risk for drug-related problems, but the exact scope of these problems, associated risk factors and effective interventions need to be studied in this population.

## AIMS AND OUTLINE OF THIS THESIS

The main objectives of this thesis are to identify determinants for medication errors and patients at risk for adverse drug events (part I) and to evaluate the effect of clinical pharmacists' interventions to optimize pharmacotherapy (part II) in both hospitalized patients and individuals with an intellectual disability.

## Part I Determinants for medication errors and adverse drug events

In the first part of this thesis, determinants for medication errors are identified in hospitalized patients and individuals with an intellectual disability. Besides, a potential electronic trigger to detect adverse drug events in an early stage is studied.

In chapter 2 we compare the risk factors associated with medication errors resulting in patient harm with the risk factors for medication errors without harm in hospitalized patients, in order to assess whether these two types of drug-related problems share the same origin.

Older individuals with an intellectual disability may be especially at risk for prescribing errors, but data on the prevalence of prescribing errors are lacking in this population. Therefore, we study the occurrence of prescribing errors as well as determinants for these errors in this specific population in chapter 3.

Adverse drug events are not only difficult to assess in research, even in daily clinical practice health care professionals do not always recognize adverse drug events.[45, 79, 80] However, the physician may have a suspicion before an adverse drug events becomes manifest. This so called "gut feeling" is a well-known phenomenon in medicine and leads to an increase in diagnostic procedures.[81-83] Therefore, in chapter 4 we explore the association between the number of biochemical tests and the manifestation of adverse drug events .

## Part II Clinical pharmacists' interventions to optimize pharmacotherapy

The second part of this thesis focuses on possible interventions by clinical pharmacists to optimize pharmacotherapy in hospitalized patients and individuals with an intellectual disability.

Both implementation of CPOE/CDSS as well as active participation of clinical pharmacists can reduce drug-related problems in hospitalized patients. In chapter 5 the contribution of medication review by a clinical pharmacist to the detection of drug-related problems in addition to CPOE/CDSS is assessed.

The applicability of medication review using a systematic tool to reduce inappropriate prescribing in individuals with an intellectual disability and polypharmacy is evaluated in a pilot study, that is presented in chapter 6.

Physicians' acceptance of pharmacists' interventions for individual patients, identified by CPOE/CDSS, to reduce drug-related problems in daily clinical practice is studied in chapter 7. Subsequently, the experiences of physicians with pharmacists' interventions, including their self-reported reasons for acceptance and non-acceptance are addressed in chapter 8.

In the summarizing discussion, chapter 9, the main results are summarized and critically reviewed in a wider perspective. We will conclude with recommendations for patient care to optimize pharmacotherapy, based on the results of our studies, and some unresolved issues that require future research

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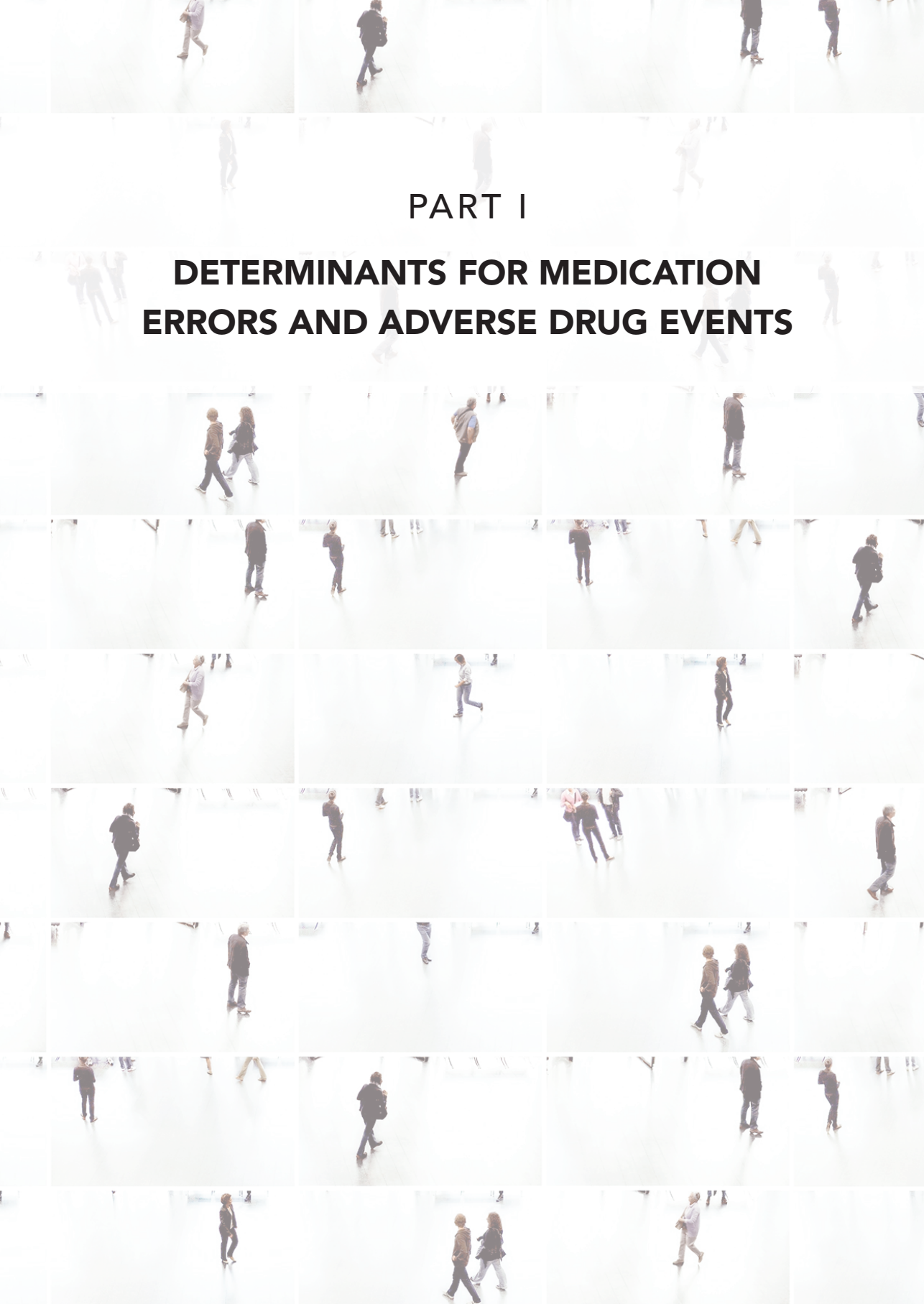

# PART I

# DETERMINANTS FOR MEDICATION ERRORS AND ADVERSE DRUG EVENTS

# 2

# Comparison of potential risk factors for medication errors with and without patient harm

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PHARMACOEPIDEMIOL DRUG SAF. 2010;19(8): 825-33

## ABSTRACT

### Objective

To compare determinants for medication errors leading to patient harm with determinants for medication errors without patient harm.

### Methods

A two-way case-control design was used to identify determinants for medication errors without harm (substudy 1) and determinants for medication errors causing harm (substudy 2). Data of patients admitted to five internal medicine wards of two Dutch hospitals during five months were collected prospectively by chart review. Medication errors were detected and classified by two pharmacists. Consensus between five pharmacists was reached on the causal relationship between medication errors and patient harm. Data analysis was performed by multivariate logistic regression.

### Results

We included 7286 medication orders, of which 3315 without errors (controls), and 5622 medication errors without harm (cases substudy 1) and 102 medication errors causing harm (cases substudy 2) were identified.

Hospital, ward and the therapeutic class anti-infectives were associated with both medication errors without harm (hospital odds ratio (OR) 1.40; 95% confidence interval (CI) 1.21-1.63), TweeSteden hospital (TSh) geriatrics OR 2.03; 95% CI 1.73-2.38, TSh general internal medicine OR 1.44; 95% CI 1.23-1.69 and anti-infectives OR 1.28; 95% CI 1.06-1.56) and medication errors with harm (hospital OR 4.91; 95% CI 3.02-7.79, TSh geriatrics OR 5.76; 95% CI 2.52-13.15, TSh general internal medicine OR 6.51; 95% CI 2.82-15.02 and anti-infectives OR 4.20; 95% CI 2.24-7.90).

### Conclusions

This study shows that organizational determinants (hospital, ward) are comparable for medication errors with and without harm. For conclusions on patient- and medication related determinants studies with larger sample sizes are needed.

## INTRODUCTION

The prevalence of medication errors in hospitals is about 6% of all medication orders and approximately 10% of all medication errors is estimated to result in patient harm.[1] Whether or not a medication error results in patient harm depends on whether the error reaches the patient and when it does, on the intrinsic toxicity of the drug and the susceptibility of the patient to adverse events. Also, certain types of medication errors are more likely to cause patient harm than others, e.g. therapeutic prescribing errors result in harm more often than administrative prescribing errors do.[2-5]

Despite the fact that not all medication errors lead to patient harm, the impact of the problem of adverse drug events (ADEs) induced by such errors is rather large. The report "To err is human" showed that in the United States 2% of all admitted patients is harmed as a result of a medication error and that 7000 patients die from medication errors annually.[6] This report has led to a renewed interest of health care professionals in improving medication safety. Such improvements can be achieved by effective interventions targeted at identified risk factors that contribute to unsafe practices and potential patient harm.

Whereas preventing actual patient harm is the ultimate goal of such medication safety initiatives, medication errors are often used as a surrogate outcome measure, because these occur more frequently and are easier to detect. However, the validity of this surrogate end point has not been established and it is unknown whether the risk factors associated with medication errors causing patient harm are the same as the risk factors associated with medication errors that do not cause harm. Therefore, we performed a study to compare the determinants for medication errors resulting in patient harm and the determinants for medication errors not resulting in harm.

## METHODS

### Design and setting

The design of the current study is a two-way case-control study. In a first substudy (1st way) medication orders with errors not leading to patient harm (cases) were compared to medication orders without errors (controls). This first substudy aimed to identify determinants for medication errors not leading to patient harm. In the second substudy (2nd way) medication orders with errors leading to patient harm (cases) were again compared to the same medication orders without errors (controls) to identify determinants for medication errors leading to patient harm. Subsequently, determinants that were identified in the first substudy were compared with determinants identified in the second substudy.

This study is part of the POEMS study on the effect of a Computerized Physician Order Entry (CPOE) system on Medication Safety and associated costs.[5, 7, 8] The POEMS study is a prospective intervention study, performed in two medical wards (one geriatric and one general internal medicine ward) of the 600 bed teaching hospital "TweeSteden" (TSh) in Tilburg and Waalwijk and three medical wards (two general internal medicine wards and one gastroenterology/rheumatology ward) of the 1300 bed University Medical Center in Groningen (UMCG), the Netherlands. The current study uses data of the period before the introduction of the CPOE-system. The process of medication ordering and administration consisted of a hand-written system: physicians prescribed medication orders on charts and nurses transcribed these medication orders on administration charts. Therefore, clinical decision support could not be provided to physicians at the time of prescribing medication.

### Patients

From July through November 2005 all patients admitted to the study wards for more than 24 hours were included. Patients received written information about the study after which they could object to inclusion. A waiver of the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of normal hospital care and routine of quality improvement and assurance.

### Data collection

During ward visits the investigators prospectively extracted patients' characteristics (age, sex, weight and length) and data on diseases (medical history, reasons for admission and diagnoses) and adverse events (i.e. untoward medical occurrences which do not have to have a causal relationship with the treatment[9]) from medical records. Medication orders issued during hospitalisation were collected by reviewing medication order charts and administration charts. For ethical reasons, the physician was informed in case of potentially life threatening errors that were discovered during the process of data collection. These errors were not excluded from the study.

### Classification of prescribing and transcribing errors

Medication errors were identified and categorized by two pharmacists according to the classification scheme for medication errors developed by the Dutch Association of Hospital Pharmacists.[10] During a pilot phase in the UMCG the two pharmacists were trained together to extract and classify medication errors uniformly. The classification distinguishes prescribing, transcribing, dispensing, administering and "across settings" errors. In this study only prescribing and transcribing errors were recorded. Prescribing errors are subdivided into administrative errors (errors on readability, patient data, ward and prescriber data, drug name, dosage form and route of administration), dosing errors (errors on strength, frequency, dosage, length of therapy and directions for use) and therapeutic errors (interactions, contra-

indications, incorrect mono-therapy, duplicate therapy and errors on therapeutic drug monitoring or laboratory monitoring). Inappropriate drug choices were not actively assessed and were only taken into account when they were obvious. Transcribing errors are defined as errors in the process of interpreting, verifying and transcribing of medication orders.

The severity of all medication errors was assessed according to the index of the National Coordinating Council for Medication Error Reporting and Preventing (NCC MERP), which categorises medication errors into nine categories (A-I) based on severity of related patient outcomes (table 1).[11] In this study, medication errors were divided into errors that did not lead to patient harm (NCC MERP category B up to D) and errors that did lead to harm (NCC MERP category E up to I).

**Table 1:** NCC MERP Categories

| Category | | Content |
|---|---|---|
| A | No harm | Circumstances or events that have the capacity to cause error |
| B | | An error occurred but the error did not reach the patient |
| C | | An error occurred that reached the patient but did not cause patient harm |
| D | | An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm |
| E | Patient harm | An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention |
| F | | An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization |
| G | | An error occurred that may have contributed to or resulted in permanent patient harm |
| H | | An error occurred that required intervention necessary to sustain life |
| I | | An error occurred that may have contributed to or resulted in the patient's death |

## Patient harm

Patient harm was defined as a preventable adverse drug event (pADE) which is an adverse drug event (ADE) that occurred due to a medication error with a possible or probable causal relationship with the medication error. To assess this relationship an algorithm was developed, based on the NCC MERP index and the Yale algorithm.[5, 11, 12] Our combined algorithm was described in detail and validated in a previous publication.[5] The Yale algorithm (table 2) assesses the causality of the association between a drug and an adverse event. In our algorithm the first three items of the Yale algorithm were used: knowledge about the relation between the drug and the event, the presence of underlying clinical conditions which could be responsible for the event and the timing of the event. The causal relations between all medication errors made and the adverse events extracted from the medical records were assessed by five pharmacists. After individual assessment consensus was reached for all cases on both causality and severity. The causal relationship could be

**Table 2:** Simplified Yale algorithm (JAMA 1979;242:623-632)

| | +1 | 0 | -1 | Score |
|---|---|---|---|---|
| **Axis 1** | Adverse event is well accepted as ADR to suspected drug. | Adverse event is not well known or drug is new. | Adverse event previously unreported as ADR to well-known drug. | |
| **Axis 2** | a) No good alternative candidate (score +2) b) Otherwise unexplained exacerbation or recurrence of underlying illness (score +1) | Alternative candidate(s) exist, but no good ones. | Good alternative candidate. | |
| **Axis 3** | Timing as expected for ADR for this adverse event - drug pair. | Timing equivocal or non-assessable | Timing inconsistent for ADR for this adverse event - drug pair (score -2) | |
| | | | **Total score** | |

Score < 0: ADR is unlikely
Score ≥ 0 and ≤ 3: ADR is possible
Score = 4: ADR is probable
Abbreviations: ADR, adverse drug reaction

defined as unlikely (score < 0), possible (score ≥ 0 and ≤ 3) or probable (score = 4). An event was defined as patient harm when consensus was reached on a possible or probable relationship with the medication error. Earlier we described the interobserver reliability on the presence of a preventable ADE and the severity of the preventable ADE assessed with the combined algorithm.[5]

## Determinants

Determinants for medication errors or (preventable) ADEs that were identified in previous studies were included, provided that the data could be extracted from medical records or medication orders.[1-4, 13-23] Potential determinants of medication errors with and without patient harm that were studied were organizational characteristics (hospital, ward, transfer from another hospital ward or care institution, length of stay and readmission to study ward during study period), patient characteristics (gender, age, renal impairment (defined as creatinine clearance ≤ 50 ml/min during hospitalization) and the number of medication orders per patient during hospital stay), characteristics of the medication order (weekday of prescription, dosage frequency less than once daily and route of administration) and the therapeutic area of the medication (identified by Anatomical-Therapeutic- Chemical (ATC) code).

## Data analysis

All data were processed with MS Access 2003 and analysed with SPSS version 16.0.

Determinants for medication errors that did not lead to patient harm were identified by comparing medication orders containing these errors with medication orders without errors (substudy 1). Determinants for medication errors that resulted in patient harm were identified by comparing medication orders containing these errors with medication orders without errors (substudy 2). Univariate logistic regression analysis was performed with the medication order as unit of analysis. Multiple errors could have been made in one medication order and analysis was performed for each medication error separately.

For determinants that were statistically significantly associated ($p<0.05$) with errors in the univariate analysis, a multivariable logistic regression analysis was performed using a manual stepwise forward logistic regression model. Determinants were consecutively entered into the model and when they changed the beta coefficient with at least 10% their contribution was considered relevant and the determinant remained in the model. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Determinants that were significantly associated with medication errors without harm in substudy 1 were compared to determinants for medication errors leading to patient harm identified in substudy 2.

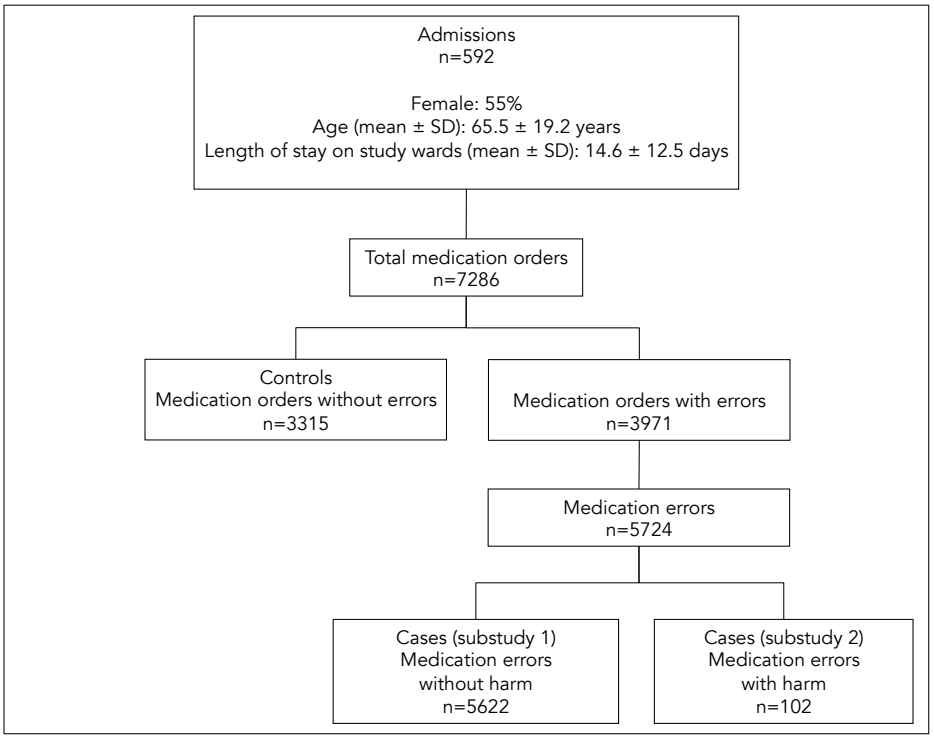


**Figure 1:** Patient characteristics, medication orders and medication errors

## RESULTS

During data collection 558 patients were included and four patients were excluded from the study due to objection to inclusion. Since 28 patients were re-admitted once and three patients were re-admitted twice, 592 admissions were included in the study. During these admissions 7286 medication orders were prescribed of which 3315 contained no error (controls). In the other 3971 medication orders a total of 5724 medication errors were identified of which 5622 did not cause patient harm (cases substudy 1) and 102 resulted in patient harm (cases substudy 2) (Figure 1). Nine medication errors were considered serious enough to require an intervention by the investigators to preclude harm. These errors were classified as errors that did not result in patient harm, but which required interventions to preclude harm (NCC MERP category D).

**Table 3:** Organisational characteristics associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

| | | | Medication errors without harm (substudy 1) | | | | |
|---|---|---|---|---|---|---|---|
| **Potential determinant** | **Controls n (%)** | | **Cases n (%)** | | **OR** | **95% CI** | **$OR_{adj}$** | **95% CI** |
| Hospital | | | | | | | | |
| TSh (UMCG is reference) | 1459 | (44.0) | 3468 | (61.7) | **2.05** | **1.88-2.24** | **1.40[1]** | **1.21-1.63** |
| Ward | | | | | | | | |
| UMCG General internal medicine | 732 | (22.1) | 904 | (16.1) | ref | | ref | |
| UMCG Gastroenterology/ rheumatology | 1124 | (33.9) | 1250 | (22.2) | 0.90 | 0.79-1.02 | 0.93[3] | 0.79-1.08 |
| TSh Geriatrics | 796 | (24.0) | 2250 | (40.0) | **2.29** | **2.02-2.60** | **2.03[3]** | **1.73-2.38** |
| TSh General internal medicine | 663 | (20.0) | 1218 | (21.7) | **1.49** | **1.30-1.70** | **1.44[3]** | **1.23-1.69** |
| Transfer from: (n=8255/ n=3056) | | | | | | | | |
| Home (ref) | 1566 | (52.7) | 3175 | (60.1) | ref | | ref | |
| Another hospital ward | 254 | (8.5) | 446 | (8.4) | 0.87 | 0.73-1.02 | **0.68[5]** | **0.58-0.81** |
| Care institution | 1151 | (38.7) | 1663 | (31.5) | **0.71** | **0.65-0.79** | **0.86[5]** | **0.78-0.96** |
| Length of stay (days, mean ± SD)* | 19.2 ± 15.5 | | 22.2 ± 17.0 | | **1.01** | **1.01-1.02** | **1.02[6]** | **1.01-1.02** |
| Readmission | 233 | (7.0) | 360 | (6.4) | 0.91 | 0.76-1.07 | | |

Figures in bold are statistically significant
Abbreviations: OR, odds ratio; 95 %CI, 95% confidence interval; $OR_{adj}$ , adjusted odds ratio; TSh, TweeSteden hospital; UMCG, University Medical Center Groningen; ref, reference
1: Ward, transfer and day of prescription contributed significantly to the model
2: No confounding factors were identified
3: Transfer, length of stay, age group, renal impairment, number of medication orders, day of prescription and pharmacotherapeutic area contributed significantly to the model
4: Age and pharmacotherapeutic area contributed significantly to the model
5: Hospital, ward and length of stay contributed significantly to the model
6: Number of medication orders contributed significantly to the model
* Analyzed as a continuous variable

Details of the univariate and multivariate analysis of organizational characteristics, patient characteristics, characteristics of the medication order and the therapeutic area are presented in Tables 3-6.

After multivariate analysis, the following determinants were significantly associated with medication errors without patient harm: hospital, ward, transfer of patient, length of hospital stay, number of medication orders per patient during hospital stay, weekday of the prescription, route of administration and the therapeutic classes cardiovascular tract, genitourinary system and hormonal system, hormonal systemic therapy, anti-infectives, musculoskeletal system, nervous system and respiratory tract. Of these determinants the following were also statistically significantly associated with medication errors with harm: hospital, ward and therapeutic class anti-infectives.

All other determinants that were statistically significantly associated with medication errors without harm (transfer of patient, length of hospital stay, number of medication orders per patient, day of prescription, route of administration and the other therapeutic

| Medication errors with harm (substudy 2) | | | | | |
|---|---|---|---|---|---|
| Cases n (%) | | OR | 95% CI | $OR_{adj}$ | 95% CI |
| 81 | (79.4) | **4.91** | **3.02-7.97** | **4.91**[2] | **3.02-7.97** |
| 7 | (6.9) | ref | | ref | |
| 14 | (13.7) | 1.30 | 0.52-3.24 | 1.73[4] | 0.68-4.41 |
| 49 | (48.0) | **6.44** | **2.90-14.30** | **5.76**[4] | **2.52-13.15** |
| 32 | (31.4) | **5.05** | **2.21-11.51** | **6.51**[4] | **2.82-15.02** |
| 56 | (59.6) | ref | | | |
| 9 | (9.6) | 0.99 | 0.48-2.02 | | |
| 29 | (30.9) | 0.71 | 0.45-1.11 | | |
| 20.4 ± 11.7 | | 1.00 | 0.99-1.02 | | |
| 8 (7.8) | (7.8) | 1.13 | 0.54-2.35 | | |

**Table 4:** Patient characteristics associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

| | Medication errors without harm (substudy 1) | | | | | |
|---|---|---|---|---|---|---|
| **Potential determinant** | **Controls n (%)** | **Cases n (%)** | **OR** | **95% CI** | **$OR_{adj}$** | **95% CI** |
| Female gender (male is reference) | 1780 (53.7) | 2990 (53.2) | 0.98 | 0.90-1.07 | | |
| Age (years, mean ± SD)* | 67.1 ± 17.8 | 70.8 ± 16.8 | **1.01** | **1.01-1.02** | 1.00[1] | 1.00-1.01 |
| <50 years | 605 (18.3) | 778 (13.8) | ref | | ref | |
| 50 to 64 years | 668 (20.2) | 882 (15.7) | 1.03 | 0.89-1.19 | 1.00[3] | 0.85-1.18 |
| 65 to 79 years | 1053 (31.8) | 1859 (33.1) | **1.38** | **1.21-1.56** | 0.99[3] | 0.84-1.17 |
| ≥ 80 years | 989 (29.8) | 2103 (37.4) | **1.65** | **1.45-1.88** | 1.02[3] | 0.85-1.23 |
| Renal impairment | 1700 (51.3) | 3176 (56.5) | **1.23** | **1.13-1.34** | 1.03[5] | 0.92-1.16 |
| Number of medication orders (mean ± SD)* | 18.2 ± 10.7 | 19.2 ± 17.0 | **1.01** | **1.00-1.01** | **0.99**[6] | **0.99-1.00** |
| Polyfarmacy (>4) | 3253 [§] (98.1) [§] | 5534 (98.4) | 1.20 | 0.86-1.66 | | |

Figures in bold are statistically significant
Abbreviations: OR, odds ratio; 95 %CI, 95% confidence interval; $OR_{adj}$ , adjusted odds ratio
1: Hospital, ward, length of stay and pharmacotherapeutic area contributed significantly to the model
2: Hospital contributed significantly to the model
3: Hospital, ward, transfer, length of stay, renal impairment, number of medication orders, day of prescription, route of administration and pharmacotherapeutic area contributed significantly to the model
4: Hospital, ward and pharmacotherapeutic area contributed significantly to the model
5: Hospital, ward, transfer, length of stay, age, number of medication orders, day of prescription, route of administration and pharmacotherapeutic area contributed significantly to the model
6: Hospital, ward, transfer, length of stay, day of prescription, route of administration and pharmacotherapeutic area contributed significantly to the model
* Analyzed as a continuous variable
[§] Dummy variables included

classes) showed no association with medication errors with harm in the univariate analysis already, had insufficient cases per category to analyze the association or showed a different trend in the odds ratio. No determinants for medication errors leading to harm were identified that had not been identified as determinant for medication errors without harm.

## DISCUSSION

This study is the first study on the comparison of determinants for medication errors with and without consequent patient harm. Hospital, ward and the therapeutic class of anti-infectives were shown to be determinants for both types of medication errors.

In this study relatively few medication errors causing patient harm were identified, despite the collection of more than 7000 medication orders during five months of daily ward visits. This main limitation of our study may explain why many of the determinants that were identified in the multivariate analysis for medication errors without harm, were non-significant in the univariate analysis for medication errors with harm.

| Medication errors with harm (substudy 2) | | | | | |
|---|---|---|---|---|---|
| Cases n (%) | | OR | 95% CI | $OR_{adj}$ | 95% CI |
| 47 | (46.1) | 0.74 | 0.50-1.10 | | |
| 74.1 ± 14.8 | | **1.03** | **1.01-1.04** | 1.01[2] | 1.00-1.03 |
| 9 | (8.8) | ref | | ref | |
| 12 | (11.8) | 1.21 | 0.51-2.89 | 1.35[4] | 0.56-3.26 |
| 38 | (37.3) | **2.43** | **1.17-5.05** | 1.77[4] | 0.81-3.90 |
| 43 | (42.2) | **2.92** | **1.42-6.04** | 1.74[4] | 0.76-4.02 |
| 61 | (59.8) | 1.41 | 0.95-2.11 | | |
| 18.3 ± 9.1 | | 1.00 | 0.98-1.02 | | |
| 103[§] | (99.0)[§] | 1.99 | 0.27-14.52 | | |

The determinants hospital and ward point in the same direction, namely that errors (either with or without harm) probably occur more often in the TSh than in the UMCG. Thus, even after correction for case-mix, it remains likely that the personnel or local processes influence the prevalence of errors, irrespective of the outcome.

Therefore, it may be concluded that for these organizational determinants, medication errors are an acceptable surrogate outcome measure for patient harm. This corresponds with findings of previous studies separately showing that organizational determinants are linked to respectively medication errors and pADEs. [2, 4, 14, 16, 19, 21]

Differences between the two hospitals and wards might be explained by differences in training of the physicians.[1, 16, 19, 21, 24, 25] The UMCG is a university tertiary care teaching hospital while the TSh is a secondary care teaching hospital, where less education may lead to more errors.

Due to the limited power of our study for medication errors leading to harm, definite conclusions on determinants that are more patient- or medication-related can not be drawn, with the possible exception of anti-infectives. The association between anti-infectives and errors might be explained by the fact that choosing the right anti-infective for an

**Table 5:** Characteristics of the medication order associated with medication errors with and without patient Tharm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

| | Medication errors without harm (substudy 1) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Potential determinant** | **Controls n (%)** | **Cases n (%)** | **OR** | **95% CI** | **$OR_{adj}$** | **95% CI** |
| Day of prescription (n=8899/3398) | | | | | | |
| Monday | 631 (19.1) | 959 (17.1) | ref | | ref | |
| Tuesday | 559 (17.0) | 871 (15.5) | 1.03 | 0.89-1.19 | 1.03[1] | 0.88-1.20 |
| Wednesday | 557 (16.9) | 971 (17.3) | 1.15 | 0.99-1.33 | 1.10[1] | 0.94-1.27 |
| Thursday | 530 (16.1) | 951 (17.0) | **1.18** | **1.02-1.37** | 1.08[1] | 0.93-1.26 |
| Friday | 587 (17.8) | 1120 (20.0) | **1.26** | **1.09-1.45** | **1.22[1]** | **1.05-1.41** |
| Saturday | 203 (6.2) | 352 (6.3) | 1.14 | 0.93-1.40 | **1.28[1]** | **1.04-1.57** |
| Sunday | 230 (7.0) | 378 (6.7) | 1.08 | 0.89-1.31 | 1.17[1] | 0.96-1.43 |
| Weekend (weekdays are reference) | 433 (13.1) | 730 (13.0) | 0.99 | 0.87-1.13 | | |
| Dosage frequency < once daily | 84 [§] (2.5) [§] | 163 (2.9) | 1.16 | 0.89-1.52 | | |
| Route of administration | | | | | | |
| Oral | 2346 (70.8) | 3701 (65.8) | ref | | ref | |
| Topical | 35 (1.1) | 94 (1.7) | **1.70** | **1.15-2.52** | 2.13[2] | 0.99-4.62 |
| Inhalation | 66 (2.0) | 209 (3.7) | **2.01** | **1.52-2.66** | 1.17[2] | 0.71-1.92 |
| Dermal | 19 (0.6) | 123 (2.2) | **4.10** | **2.52-6.67** | **3.31[2]** | **1.31-8.41** |
| Parenteral | 758 (22.9) | 1121 (19.9) | 0.94 | 0.84-1.04 | 1.04[2] | 0.91-1.18 |
| Rectal | 62 (1.9) | 280 (5.0) | **2.86** | **2.16-3.79** | **3.19[2]** | **2.33-4.37** |
| Transdermal | 29 (0.9) | 55 (1.0) | 1.20 | 0.76-1.89 | 0.91[2] | 0.52-1.57 |
| Sublingual | 0 (0) | 39 (0.7) | [†] | | [†] | |

Figures in bold are statistically significant
Abbreviations: OR, odds ratio; 95 %CI, 95% confidence interval; $OR_{adj}$ , adjusted odds ratio ref, reference
1: Hospital, ward, length of stay, route of administration and pharmacotherapeutic area contributed significantly to the model
2: Hospital, ward, transfer, length of stay, number of medication orders, day of prescription and pharmacotherapeutic area contributed significantly to the model
[†] Statistical analysis not possible due to insufficient data
[§] Dummy variables included

infection could be more difficult than choosing drugs for other indications. Moreover, the dosage of most anti-infectives must be adjusted according to the patient's renal function, so dosage errors are made more easily. Theoretically it seems likely that for medication errors leading to patient harm, specific determinants may be identified that reflect either the vulnerability of the patient to experience pADEs or the intrinsic toxicity of the medication. Anti-infectives, for example, have a great intrinsic toxicity and are prescribed to acutely ill patients, who are very susceptible for ADEs. This might explain the association between anti-infectives and ADEs. [1-3, 14, 17, 19, 22, 23] Again, the determinants identified in our study for medication errors without harm were identified in other studies, both for medication errors (identified determinants were number of medication orders per patient,

| Medication errors with harm (substudy 2) | | | |
|---|---|---|---|
| Cases n (%) | | OR | 95% CI |
| 18 | (17.8) | ref | |
| 15 | (14.9) | 0.94 | 0.47-1.88 |
| 21 | (20.8) | 1.32 | 0.70-2.51 |
| 20 | (19.8) | 1.32 | 0.70-2.53 |
| 18 | (17.8) | 1.08 | 0.55-2.09 |
| 7 | (6.9) | 1.21 | 0.50-2.94 |
| 2 | (2.0) | 0.31 | 0.07-1.32 |
| 9 | (8.9) | 0.65 | 0.32-1.29 |
| 1 § | (1.0) § | 0.37 | 0.05-2.71 |
| 72 | (70.6) | ref | |
| 1 | (1.0) | 0.93 | 0.13-6.89 |
| 4 | (3.9) | 1.98 | 0.70-5.57 |
| 0 | (0) | † | |
| 23 | (22.5) | 0.99 | 0.61-1.59 |
| 2 | (2.0) | 1.05 | 0.25-4.38 |
| 0 | (0) | † | |
| 0 | (0) | † | |

route of administration and pharmacotherapeutic area[1, 18, 20]) and for (preventable) ADEs (identified determinants were among others number of medication orders per patient and therapeutic area[1, 14, 17, 19, 20, 22, 23]). However, none of these previous studies compared the determinants for medication errors without harm with the determinants for medication errors leading to patient harm.

A number of explanations for identified associations between specific determinants and the risk of medication errors without harm can be given. First of all, transfer of patients from home was associated with medication errors without harm in this study. Because no medication reconciliation was performed at admission, errors can be made more easily when patients are admitted from home, compared to transfers between hospital wards or

**Table 6:** Therapeutic areas associated with medication errors with and without patient harm after univariate logistic regression (odds ratios) and multivariate logistic regression (adjusted odds ratios)

| | Medication errors without harm (substudy 1) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Potential determinant** | **Controls n (%)** | **Cases n (%)** | **OR** | **95% CI** | **$OR_{adj}$** | **95% CI** |
| Therapeutic area (ATC-code) | | | | | | |
| Gastrointestinal tract (A) | 835 (25.2) | 1166 (20.7) | ref | | ref | |
| Blood system (B) | 478 (14.4) | 691 (12.3) | 1.04 | 0.89-1.20 | 1.13[1] | 0.95-1.33 |
| Cardiovascular tract (C) | 716 (21.6) | 831 (14.8) | **0.83** | **0.73-0.95** | **0.82[1]** | **0.71-0.94** |
| Dermatologicals (D) | 24 (0.7) | 124 (2.2) | **3.70** | **2.37-5.78** | 1.45[1] | 0.59-3.53 |
| Genitourinary system and sex hormones (G) | 40 (1.2) | 35 (0.6) | **0.63** | **0.40-1.00** | **0.59[1]** | **0.36-0.96** |
| Hormonal systemic therapy (H) | 126 (3.8) | 249 (4.4) | **1.42** | **1.12-1.79** | **1.63[1]** | **1.26-2.10** |
| Anti-infectives (J) | 264 (8.0) | 454 (8.1) | **1.23** | **1.03-1.47** | **1.28[1]** | **1.06-1.56** |
| Cancer therapy (L) | 47 (1.4) | 47 (0.8) | 0.72 | 0.47-1.08 | 0.81[1] | 0.49-1.35 |
| Musculo-skeletal system (M) | 86 (2.6) | 172 (3.1) | **1.43** | **1.09-1.89** | **1.62[1]** | **1.20-2.20** |
| Nervous system (N) | 537 (16.2) | 1415 (25.2) | **1.89** | **1.65-2.16** | **1.85[1]** | **1.60-2.14** |
| Antiparasitic products, insecticides and repellents (P) | 13 (0.4) | 5 (0.1) | **0.28** | **0.10-0.78** | 0.40[1] | 0.14-1.18 |
| Respiratory tract (R) | 104 (3.1) | 324 (5.8) | **2.23** | **1.76-2.83** | **2.30[1]** | **1.54-3.43** |
| Sensory organs (S) | 28 (0.8) | 68 (1.2) | **1.74** | **1.11-2.73** | 0.92[1] | 0.38-2.21 |
| Various (V) | 13 (0.4) | 36 (0.6) | **1.98** | **1.05-3.76** | 1.11[1] | 0.51-2.42 |
| Unknown | 4 (0.1) | 5 (0.1) | 0.90 | 0.24-3.34 | 1.02[1] | 0.23-4.59 |

Figures in bold are statistically significant

Abbreviations: OR, odds ratio; 95 %CI, 95% confidence interval; $OR_{adj}$ , adjusted odds ratio; ref, reference

1: Hospital, ward, transfer, length of stay, day of prescription and route of administration contributed significantly to the model

2: Hospital, ward and age contributed significantly to the model

† Statistical analysis not possible due to insufficient data

other affiliated care institutions when actual medication is exchanged in a specified way between health care professionals.

Prolonged length of stay increased the risk of a medication error without harm. In the handwritten system the medication orders have to be transcribed again by nurses on a new administration chart when an old chart is completed, which can cause transcribing errors, which may explain this increased risk of medication errors.

After correcting for confounding factors, an increasing number of medication orders decreases the risk of medication errors without harm slightly. This is not consistent with previous studies and can possibly be explained by extra attention of physicians to patients who use more drugs.[15] Medication orders prescribed on Friday and Saturday were at risk for medication errors without harm, which can be explained by a higher workload and less knowledge about the patient's condition, because of staff changes and fewer physicians being present.[4, 16, 19, 21] With dermal preparations, directions for use, for example the site of

| Medication errors with harm (substudy 2) | | | | | |
|---|---|---|---|---|---|
| Cases n (%) | | OR | 95% CI | $OR_{adj}$ | 95% CI |
| 20 | (19.6) | ref | | ref | |
| 14 | (13.7) | 1.22 | 0.61-2.44 | 1.22 | 0.60-2.45 |
| 10 | (9.8) | 0.58 | 0.27-1.25 | 0.48 | 0.22-1.03 |
| 0 | (0) | † | | † | |
| 1 | (1.0) | 1.04 | 0.14-7.97 | 0.84 | 0.11-6.51 |
| 1 | (1.0) | 0.33 | 0.04-2.49 | 0.37 | 0.05-2.77 |
| 23 | (22.5) | **3.64** | **1.97-6.73** | **4.20**[2] | **2.24-7.90** |
| 0 | (0) | † | | † | |
| 2 | (2.0) | 0.97 | 0.22-4.22 | 1.08 | 0.25-4.75 |
| 25 | (24.5) | **1.94** | **1.07-3.53** | 1.62[2] | 0.89-2.98 |
| 0 | (0) | † | | † | |
| 5 | (4.9) | 2.01 | 0.74-5.46 | 2.15 | 0.78-5.94 |
| 1 | (1.0) | 1.49 | 0.19-11.51 | 1.56 | 0.19-12.50 |
| 0 | (0) | † | | † | |
| 0 | (0) | † | | † | |

application, were often missing on the prescription. This is an explanation for the high number of errors without harm.[18]

For all of the determinants that were associated with medication errors without harm, it can be suggested that most of these errors were administrative errors which result in patient harm less often than therapeutic errors.[7]

Although most of the determinants identified in this study can not be influenced by health care professionals directly to prevent patient harm, they give a first impression of risk departments, risk processes and risk medication and they are suitable to provide an answer to the main study aim. However, future studies should also focus on determinants that are more likely to be influenced by health care professionals.

Besides the small sample size of medication errors leading to harm, this study has several other limitations. First, only five wards in two hospitals were studied, so the results cannot be generalized to other medical specialties, wards or hospitals. Second, the medication ordering was done in the context of a handwritten-system. Implementation of a comput-

erized physician order entry system with clinical decision support could change the risk factors for medication errors. Third, risk factors for medication errors and consequent harm could differ between continuation of pre-admission treatment and hospital-initiated drugs. Because it wasn't necessary to define pre-admission treatment in the POEMS-study and medication reconciliation was not performed, this determinant could not be included in this study either. However, precribing errrors and transcribing errors in medication orders for continuation of pre-admission treatment were assessed. Finally, only prescribing and transcribing errors were considered in this study. To provide a full overview of the potential determinants for medication errors with and without harm distribution errors, administration errors and "across settings" errors should also be studied.

The main strength of this study is the epidemiological approach to identify risk factors by calculating odds ratios, whereas many other studies used error frequencies. Moreover, we established the actual outcome of the medication error instead of the potential harm an error could cause which many other studies did and our study is the first comparing determinants for medication errors without and with patient harm.

Future research with a larger sample size of medication errors leading to patient harm is recommended. These future studies should also take into account other types of medication errors and include more organizational determinants (such as the use of electronic prescribing) and patient related factors (like the reason for admission and comorbidities).

To conclude, medication errors resulting in harm and medication errors without harm have some determinants in common, which are mainly at the organizational level. Therefore, the present study gives a first direction about the validity of medication errors as a surrogate outcome measure when looking at these organizational aspects. More determinants could possibly be identified in studies with larger sample sizes, which may identify specific patient- and medication-related determinants for medication errors leading to patient harm.

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# 3

# Prescription errors in older individuals with an intellectual disability: prevalence and risk factors in the Healthy Ageing and Intellectual Disability Study

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## ABSTRACT

### Background

Prescribing pharmacotherapy for older individuals with an intellectual disability (ID) is a complex process, possibly leading to an increased risk of prescription errors.

### Objective

The objectives of this study were (1) to determine the prevalence of older individuals with an intellectual disability with at least one prescription error and (2) to identify potential risk factors for these prescription errors (age, gender, body mass index (BMI), frailty index, level of intellectual disability and living situation).

### Methods

The study population consisted of 600 older (≥50 years) individuals with an ID using one or more drugs who were randomly selected from the study cohort of the Healthy Ageing and Intellectual Disability (HA-ID) study. The medication used at the time of measurement was screened for errors by a hospital pharmacist/clinical pharmacologist and a Master's student pharmacy using consensus methodology. Participants with one or more prescription errors were compared to participants without prescription errors by multivariate logistic regression to identify potential risk factors.

### Results and conclusions

The prevalence of individuals with one or more prescription errors was 47.5% (285 of 600 individuals; 95% confidence interval (CI) 43-52%). Relevant errors, defined as errors that actually do require a change of pharmacotherapy, were identified in 26.8% of the individuals (161 of 600 individuals; 95% CI 23-30%). Higher age (adjusted odds ratio ($OR_{adj}$) 1.03; 95% CI 1.01-1.06), less severe intellectual disability (moderate: $OR_{adj}$ 0.48; 95% CI 0.31-0.74 and severe: $OR_{adj}$ 0.56; 95% CI 0.32-0.98), higher BMI ($OR_{adj}$ 1.04; 95% CI 1.01-1.08), higher frailty index (0.39-0.54: $OR_{adj}$ 2.4; 95% CI 1.21-4.77 and ≥0.55: $OR_{adj}$ 3.4; 95% CI 1.03-11.02), polypharmacy ($OR_{adj}$ 8.06; 95% CI 5.59-11.62) and use of medicines acting on the central nervous system ($OR_{adj}$ 3.34; 95% CI 2.35-4.73) were independently associated with the occurrence of prescription errors. Interventions targeted to high risk patients should be designed and implemented to improve pharmacotherapy in older individuals with an intellectual disability.

## INTRODUCTION

Inappropriate prescribing of pharmacotherapy occurs in about 20 to 40% of older individuals in the general population.[1-3] Polypharmacy, i.e. concomitant use of five or more drugs, is also very common among these older people[1, 4] and has been identified as a risk factor for the occurrence of prescription errors.[1]

The life expectancy of older individuals with an intellectual disability (ID) is increasing and age-related frailty seems to start at a younger age.[5] As a result, polypharmacy is very common among individuals with an intellectual disability aged 50 years and older. For example, antipsychotics, that have been associated with inappropriate prescriptions in older individuals in general[1], are frequently used by individuals with an ID to treat psychiatric diseases and behavioral problems.[6] Additionally, chronic somatic diseases, such as epilepsy[7] and gastro-esophageal reflux disease[8], frequently require pharmacotherapy. Other factors that may increase the complexity of prescribing drugs to older individuals with an ID are the often atypical symptoms of disease[9]; the impaired ability to communicate about disease and effectiveness of pharmacotherapy[9]; and the limited evidence for treatment of mental and behavioral problems with psychotropic drugs.[10]

As a result, older individuals with an ID may be especially at risk of prescription errors. However, the prevalence of prescription errors and risk factors for such errors have not been established in this population. Therefore, the objectives of this study were (1) to determine the prevalence of older individuals with an intellectual disability with at least one prescription error and (2) to identify potential risk factors for these prescription errors.

## METHODS

### Design

A cross-sectional study was performed to determine the prevalence of older individuals with an intellectual disability with at least one prescription error and to identify potential risk factors for these errors.

### Setting and study population

The included research population in this study consisted of older individuals with an ID using one or more medicines who participated in the study titled "Healthy Ageing and Intellectual Disability" (HA-ID).[11]

The cohort from the Erasmus MC HA-ID study [11] consists of 1050 clients with an ID, defined as an intelligence quotient of 70 and lower, aged 50 years and older, from three Dutch care organizations (Abrona, Huis ter Heide; Ipse de Bruggen, Zwammerdam; Amarant, Tilburg). The included population varies in ID level, living situation, mobility and

level of care. The population in the HA-ID study is considered representative for the total population of older individuals with an ID using formal ID services in the Netherlands.[11]

For the current study 187 individuals with prescription errors and 187 controls were necessary to be able to detect odds ratios of at least 2, with alpha=0.05 and power=0.8. To obtain these numbers 600 individuals were randomly selected from the HA-ID cohort.

Since this study did not affect patient integrity, a waiver from the Medical Ethics Committee was obtained.

## Data collection

The cross-sectional data of the HA-ID study were collected between March 2009 and March 2010. Participant characteristics (gender, age, level of intellectual disability, body mass index (BMI), living situation), medical data on co-morbidities and actual medication orders were obtained from the care-providing organizations and the responsible physician (i.e. a general practitioner or a specialized physician for individuals with an ID) or measured by the investigators of the HA-ID study.[11]

The frailty index indicates the increased vulnerability of an individual to adverse health outcomes. We created a frailty index for older individuals with ID based on the procedure described by Searle et al.[12]

Frailty was assessed considering a list of 51 deficits, including age-related risk factors (such as falling, weight loss and hospitalization), morbidity (such as cancer, asthma/COPD, diabetes mellitus and heart failure) and disabilities (such as being unable to dress, bath or walking stairs).[13] The presence of these deficits was obtained from the medical records or measured by the investigators of the HA-ID study.[11] Subsequently, the frailty index was expressed as a ratio of present deficits to the total number of deficits considered (i.e. 51), resulting in a frailty index between 0 (no deficits) and 1 (all deficits are present). In the general older population aged 70 years and over a frailty index of 0 to 0.15 is most common.[12]

## Definition and classification of prescription errors

Prescription errors were defined as prescriptions that were not in concordance with current standards. To facilitate the detection of prescription errors, the current prescribing standards were summarized into a so called 'Good Prescribing Practice (GPP) for older individuals with an ID'. A draft version of the GPP was written by a Master's student pharmacy on the basis of literature and guidelines from the Netherlands´ Society of Physicians for People with Intellectual Disabilities[14], the Dutch College of General Practitioners[15] and the Dutch Institute for Healthcare Improvement.[16] As these guidelines also consider off-label prescribing, for example the use of antipsychotics for behavioral problems, evidence-based off-label prescribing was included in our GPP as well. A focus group, consisting of five specialized physicians for individuals with an ID and a hospital

pharmacist/ clinical pharmacologist reached consensus on the completeness and the correctness of this draft version, resulting in a final version of the GPP. For prescriptions not covered by the GPP, general handbooks on pharmacotherapy were used to assess concordance with current standards.

Prescription errors were categorized into three classes according to the classification system for medication errors developed by the Dutch Association of Hospital Pharmacists[17], namely administrative errors (such as incomplete or illegible orders), dosing errors and therapeutic errors. Because the original orders were no longer available for this study, administrative errors could not be assessed. Dosage errors and therapeutic errors were categorized into subtypes that are defined in table 1. Because we could not assess the handling of interactions and contra-indications by the physician, we regarded interactions and contra-indications that required additional monitoring as potentially relevant errors that can be managed by the physician. Besides, lacking of a maximum daily dose for medication used "as needed" and drug-drug interactions that require a specific time-window between the intake of the drugs were assessed as potentially relevant errors as well. All other errors were defined as relevant errors, i.e. errors that actually did require a change of pharmacotherapy. Since our GPP also covered off-label prescribing to this specific population, off-label prescriptions that were in concordance with the GPP were not considered as errors.

### Detection of prescription errors

A Master's student gained insight into pharmacotherapy for this population by composing the GPP and was trained to detect and classify errors by a hospital pharmacist.

Subsequently, medication orders were independently screened by the Master's student Pharmacy and a hospital pharmacist/clinical pharmacologist to identify prescription errors. In case of any discrepancies, these two assessors reached consensus on the presence of errors. In case consensus could not be reached a second experienced hospital pharmacist, assessed the error and made a final decision on the presence of an error.

### Statistical analysis

Data were analyzed using IBM SPSS Statistics 17.0. To test the representativeness of the study sample, Chi-square analysis was used to test differences between the study participants and the total HA-ID study population in gender, age, level of ID, body mass index, frailty index and living situation. Descriptive statistics were used to determine the prevalence of individuals with one or more prescription errors and the prevalence of individuals with one or more relevant prescription errors (aim 1). Univariate logistic regression analyses were performed to identify potential risk factors for all prescription errors and for relevant errors (aim 2). Potential risk factors that were studied included patient characteristics (age, gender, level of ID, BMI and frailty index), living situation (centralized setting

**Table 1:** Classification of prescription errors and examples of detected errors.

| Type of error | Relevant | Definition | Example of a detected error |
|---|---|---|---|
| Dosage errors | | | |
| Dosage too low | Yes | The drug is not being effective at producing the desired response in the prescribed dose | Sofradex eardrops 3 times a day 2 drops instead of 3-4 times a day 3 drops |
| Dosage too high | Yes | Too much of a drug is prescribed or the patient is at risk of developing a new medical condition because too much of the correct drug is being taken | Maprotilin 2 times a day 50 mg, while maximum dose for elderly is 75 mg a day |
| No maximum daily dosage for 'as needed' prescriptions | Potentially[a] | The prescribed drug should be used " as needed" (pro re nata) but the required maximum daily dosage is lacking on the prescription | Arcoxia 90mg as needed |
| Therapeutic errors | | | |
| Additional drug therapy required | Yes | The patient has a medical condition that requires the initiation of new or additional drug therapy or is at high-risk of developing a new medical condition for which additional drug therapy is indicated | Dipyridamole lacking as secondary prevention after a cerebrovascular accident |
| Unnecessary drug therapy | Yes | The patient is undergoing drug therapy that is unnecessary given his or her present condition | Furosemide use without a diagnosis of heart failure |
| Interaction | Yes | A combination of two or more drugs administered to a patient that can result in a modification of the effect of at least one drug | Concomitant use of prednisone and acetylsalicylic acid without gastric protection |
| Contra-indication | Yes | A drug that is undesired because of the medical condition of the patien | Haloperidol use in a person with Parkinson's disease |
| Duplicate therapy | Yes | The use of two or more drugs with the same ATC classification | Concomitant use of mesalazine generic product and brand product |
| Pseudo duplicate therapy | Yes | The use of two or more drugs with similar pharmacodynamic properties, which can lead to adverse drug events | Concomitant use of nitrazepam and oxazepam |
| Interaction needing monitoring | Potentially[a] | A combination of two or more drugs that requires additional monitoring to prevent adverse events | Concomitant use of levothyroxine and acenocoumarol requires additional monitoring of international normalized ratio |
| Time interaction | Potentially[a] | A combination of two or more drugs that requires a specified time-window between administrations of the drugs | Simultaneous use of calcium carbonate and alendronate requires a time-window of two hours between alendronate and calcium carbonate |
| Contra-indication needing monitoring | Potentially[a] | The medical condition of the patient requires additional monitoring during treatment with a drug | Risperidone used in a patient with epilepsy requires alertness for an increase of seizure frequency |

[a] These errors were considered as potentially relevant, assuming correct handling of the error by the physician.
ATC classification = anatomical therapeutical chemical classification system

versus community based), and medication characteristics (total number of medicines and number of drugs acting on the central nervous system (anatomical therapeutical chemical classification N)). Potential risk factors that showed a significant association ($p<0.1$) in the univariate analysis were entered in a multivariate model, using a stepwise enter method. When a potential risk factor changed the ß-coefficient with at least 10% its contribution was considered significant. Crude and adjusted odds ratios with 95% confidence intervals were calculated. Independent variables were checked for multicollinearity, using Pearson's correlation coefficient. For highly correlated determinants (>0.400) only one potential risk factor was included in the multivariate model.

## RESULTS

### Study population

Of the 1050 individuals with an ID included in the HA-ID study, 820 persons used one or more medicines at the time of inclusion of which 600 were randomly selected. In total 2773 prescriptions of these randomly selected individuals were screened for errors. Characteristics of the selected individuals and differences between this sample and the HA-ID cohort are presented in table 2. Individuals in centralized settings were slightly overrepresented in our sample. Probably, individuals living in a centralized setting have more complex disorders requiring pharmacotherapy. The frailty index significantly differed between our sample and the original cohort, but the difference was very small and not considered to be clinically relevant.

**Table 2** Characteristics of the study population and representativeness for HA-ID cohort

| Characteristic | Study population | Cohort | p-value |
|---|---|---|---|
| Age (years), mean ± SD | 61.8 ± 8.2 | 61.6 ± 8.0 | n.s. |
| Body Mass Index, mean ± SD | 27.5 ± 5.4 | 27.2 ± 5.2 | n.s. |
| Frailty Index | 0.3 ± 0.1 | 0.3 ± 0.1 | **p=0.047** |
| Female gender | 297 (49.5) | 511 (48.7) | n.s. |
| Level of ID | | | |
| Mild ID | 136 (22.7) | 254 (24.2) | n.s. |
| Moderate ID | 301 (50.2) | 506 (48.2) | n.s. |
| Severe ID | 152 (25.3) | 263 (25.7) | n.s. |
| Living situations | | | |
| Centralized setting | 365 (60.8) | 557 (53.0) | |
| Community based | 234 (39.0) | 483 (46.0) | **p=0.004** |

n.s. = not statistically significant

## Prevalence of prescription errors

In total 446 errors, including 195 relevant errors, were identified. The Master's student Pharmacy and the hospital pharmacist/clinical pharmacologist reached consensus on all errors. Frequencies of the different subtypes of identified errors are presented in table 3. Most prescription errors involved drugs acting on the nervous system (43.2% of the prescriptions with one or more errors) and cardiovascular drugs (17.5% of the prescriptions with one or more errors). Prescription errors were identified in 285 out of the 600 randomly selected individuals, resulting in a prevalence of individuals with one or more prescription errors of 47.5 % (95% confidence interval (CI) 43-52%). Relevant prescription errors were identified in 161 individuals, resulting in a prevalence of 26.8% (95% CI 23-30%).

**Table 3** Subtypes of identified errors

| Type of error | All prescription errors n=446 n (%) | Relevant errors n=195 n (%) |
|---|---|---|
| **Dosage errors** | | |
| Dosage too low | 5 (1.1) | 5 (2.6) |
| Dosage too high | 54 (12.1) | 54 (27.7) |
| No maximum daily dosage for 'as needed' prescriptions | 68 (15.3) | - |
| **Therapeutic errors** | | |
| Additional drug therapy required | 34 (7.6) | 34 (17.4) |
| Unnecessary drug therapy | 50 (11.2) | 50 (25.6) |
| Interaction | 1 (0.2) | 1 (0.5) |
| Contra-indication | 11 (2.5) | 11 (5.6 ) |
| Duplicate therapy | 3 (0.7) | 3 (1.5) |
| Pseudo-duplicate therapy | 34 (7.6) | 34 (17.4) |
| Interaction needing monitoring | 81 (18.2) | - |
| Time interaction | 34 (7.6) | - |
| Contra-indication needing monitoring | 71 (15.9) | - |

## Potential risk factors for prescription errors

Details of the univariate and multivariate analysis to identify potential risk factors for prescription errors are presented in table 4. Table 5 shows the results of the analysis for relevant errors. Frailty index and polypharmacy showed a high correlation (0.435). Therefore, these variables were not included together in the multivariate analysis to prevent multicollinearity. First, the contribution of frailty index to the model was tested. If frailty index contributed significantly to the model, polypharmacy was not included in the

**Table 4:** Potential risk factors associated with all prescription errors (potentially relevant and relevant errors) after univariate logistic regression (odds ratio) and multivariate logistic regression (adjusted odds ratio)

| Potential risk factor | Controls n=315 n (%) | Cases n=285 n (%) | OR | 90% CI | $OR_{adj}$ | 95% CI |
|---|---|---|---|---|---|---|
| Age (years, mean ± SD) | 60.5 ± 7.3 | 63.2 ± 8.9 | **1.04** | **1.03-1.06** | **1.03**[a] | **1.01-1.06** |
| Gender | | | | | | |
| Male | 162 (51.4) | 141 (49.5) | ref. | | ref. | |
| Female | 153 (48.6) | 144 (50.5) | 1.08 | 0.83-1.42 | - | - |
| Level of ID | | | | | | |
| Mild ID | 59 (19.0) | 77 (27.6) | ref. | | ref. | |
| Moderate ID | 176 (56.8) | 125 (44.8) | **0.54** | **0.39-0.77** | **0.48**[b] | **0.31-0.74** |
| Severe ID | 75 (24.2) | 77 (27.6) | **0.79** | **0.53-1.16** | **0.56**[b] | **0.32-0.98** |
| Living situation | | | | | | |
| Centralized | 181 (57.6) | 184 (64.6) | ref. | | ref. | |
| Community based | 133 (42.4) | 101 (35.4) | **0.75** | **0.57-0.99** | 0.94[c] | 0.63-1.40 |
| Body Mass Index (mean ± SD) | 26.9 ± 4.9 | 28.1 ± 5.8 | **1.04** | **1.01-1.07** | **1.04**[d] | **1.01-1.08** |
| Frailty Index | | | | | | |
| ≤0,20 | 71 (23.2) | 39 (14.3) | ref. | | ref. | |
| 0,21 - 0,38 | 172 (56.2) | 124 (45.6) | 1.31 | 0.90-1.92 | 1.11[e] | 0.65-1.88 |
| 0,39 – 0,54 | 55 (18.0) | 83 (30.5) | **2.75** | **1.78-4.25** | **2.40**[e] | **1.21-4.77** |
| ≥ 0,55 | 8 (2.6) | 26 (9.6) | **5.92** | **2.82-12.42** | **3.37**[e] | **1.03-11.02** |
| Number of medicines | | | | | | |
| No polypharmacy | 241 (76.5) | 82 (28.8) | ref. | | ref. | |
| Polypharmacy (5 or more) | 74 (23.5) | 203 (71.2) | **8.06** | **5.93-10.96** | **8.06**[d] | **5.59-11.62** |
| Use of CNS medicines | | | | | | |
| None | 164 (52.1) | 70 (24.6) | ref. | | ref. | |
| 1 or more | 151 (47.9) | 215 (75.4) | **3.34** | **2.49-4.47** | **3.34**[d] | **2.35-4.73** |

Figures in bold are statistically significant

Abbreviations: OR, odds ratio; 90%CI, 90% confidence interval; 95%CI, 95% confidence interval; $OR_{adj}$, adjusted odds ratio; ref, reference; CNS, central nervous system

[a] Body Mass Index and frailty index were included in the model

[b] Age, living situation and frailty index were included in the model

[c] Level of ID and frailty index were included in the model

[d] No confounding factors were identified

[e] Age, level of ID, living situation and Body Mass Index were included in the model

model. If frailty index did not contribute to the model, the contribution of polypharmacy was subsequently tested.

Higher age, less severe intellectual disability, polypharmacy and use of drugs acting on the nervous system showed a significant independent association with both all prescription errors and relevant errors. Higher BMI and frailty index were associated with all prescription errors only.

**Table 5:** Potential risk factors associated with relevant prescription errors after univariate logistic regression (odds ratio) and multivariate logistic regression (adjusted odds ratio)

| Potential determinant | Controls n=439 n (%) | Cases n=161 n (%) | OR | 90% CI | $OR_{adj}$ | 95% CI |
|---|---|---|---|---|---|---|
| Age (years, mean ± SD) | 61.0 ± 7.8 | 63.7 ± 9.0 | **1.04** | **1.02-1.06** | **1.04[a]** | **1.01-1.07** |
| Gender | | | | | | |
| Male | 224 (51.0) | 79 (49.1) | ref. | | ref. | |
| Female | 215 (49.0) | 82 (50.9) | 1.08 | 0.80-1.46 | - | - |
| Level of ID | | | | | | |
| Mild ID | 85 (19.7) | 51 (32.3) | ref. | | ref. | |
| Moderate ID | 231 (53.6) | 70 (44.3) | **0.51** | **0.35-0.73** | **0.46[b]** | **0.28-0.77** |
| Severe ID | 115 (26.7) | 37 (23.4) | **0.54** | **0.35-0.82** | 0.58[b] | 0.30-1.10 |
| Living situation | | | | | | |
| Centralized | 264 (60.3) | 101 (62.7) | ref. | | ref. | |
| Community based | 174 (39.7) | 60 (37.3) | 0.90 | 0.66-1.23 | - | - |
| Body Mass Index (mean ± SD) | 27.2 ± 5.1 | 28.4 ± 6.0 | **1.04** | **1.01-1.07** | 1.04[c] | 1.00-1.08 |
| Frailty Index | | | | | | |
| ≤0.20 | 83 (19.7) | 27 (17.3) | ref. | | ref. | |
| 0.21 - 0.38 | 227 (53.8) | 69 (44.2) | 0.93 | 0.61-1.44 | 0.88[d] | 0.49-1.56 |
| 0.39 - 0.54 | 90 (21.3) | 48 (30.8) | **1.64** | **1.03-2.62** | 1.76[d] | 0.86-3.57 |
| ≥ 0.55 | 22 (5.2) | 12 (7.7) | 1.68 | 0.84-3.36 | 1.12[d] | 0.37-3.37 |
| Number of medicines | | | | | | |
| No polypharmacy | 274 (62.4) | 49 (30.4) | ref. | | ref. | |
| Polypharmacy (5 or more) | 165 (37.6) | 112 (69.6) | **3.80** | **2.74-5.25** | **3.80[e]** | **2.58-5.59** |
| Use of CNS medicines | | | | | | |
| None | 194 (44.2) | 40 (24.8) | ref. | | ref. | |
| 1 or more | 245 (55.8) | 121 (75.2) | **2.40** | **1.71-3.36** | **2.67[f]** | **1.71-4.16** |

Figures in bold are statistically significant
Abbreviations: OR, odds ratio; 90%CI, 90% confidence interval; 95%CI, 95% confidence interval; ORadj, adjusted odds ratio; ref, reference
[a] Body Mass Index and frailty index were included in the model
[b] Age, Body Mass Index and frailty index were included in the model
[c] Number of medicines was included in the model
[d] Age, level of ID, Body Mass Index were included in the model
[e] No confounding factors were identified
[f] Body Mass Index was included in the model

## DISCUSSION

This study, performed in a representative population, shows that prescription errors are frequently identified in older individuals with an intellectual disability. The prevalence of individuals with prescription errors in our population was 47.5% and relevant errors were identified in 26.8% of included individuals. Higher age, less severe intellectual disability, polypharmacy and use of drugs acting on the central nervous system showed a significant

association with both all prescription errors and relevant errors. Higher BMI and frailty index were associated with all prescription errors only.

The prevalence of prescription errors is comparable to the prevalence in older individuals in general: 20% in outpatients[3] and 40% in care institutions.[1] In our study administrative prescription errors and the duration of pharmacotherapy could not be assessed. Therefore, the actual prevalence of prescription errors in this specific population may even be higher.

Higher age, BMI and polypharmacy have been identified as risk factors for prescription errors in older individuals in the general population.[1, 9] We expected that a more severe intellectual disability would be a risk factor for prescription errors due to difficulties in diagnosing health problems and dosing problems. However, individuals with moderate and severe ID experienced relatively less errors compared to individuals with a mild ID. Possibly, physicians prescribe drugs more carefully to individuals with a more severe ID, resulting in fewer errors. Besides, differences in knowledge or experience between physicians could contribute to difference in errors. Individuals with a more severe ID are being treated in centralized settings, employing specialized physicians for people with intellectual disabilities more often. These physicians are specialized in chronic multimorbidity of individuals with an ID. General practitioners, treating individuals living in a community based setting, have less experience with this specific population, which could result in more prescription errors. However, living situation was not associated with the occurrence of errors. Still, differences between individual physicians could have influenced the results. Unfortunately, characteristics of the prescribing physician could not be assessed in our study. Future studies should give more insight in the association between prescriber's characteristics and prescription errors.

Our study has several limitations. First, data on medication used by included individuals have been transcribed on a case report form by the responsible physician. These data have been transferred to an electronic database. Both steps could result in transcribing errors. To prevent a false positive result, administrative errors, that could have been a result of these transcribing errors, were not included in this study. Second, the duration of pharmacotherapy, such as long-term use of antipsychotics, which is quite common in this population,[18] could not be determined due to the cross-sectional design. As a result, the occurrence of prescription errors could be even higher in daily practice.

Third, information on the current health problems of the individuals, monitoring of potential adverse drug events and the physician's arguments to accept potential errors (such as contra-indications, drug-drug interactions, duplicate therapy and off-label prescribing not included in the GPP) were unknown in this study. Therefore, certain prescription errors might have been deliberately accepted by the physician or might have been managed by intensive monitoring of the individual. We tried to resolve this problem to define relevant errors that do require a change of pharmacotherapy.

Fourth, the consequences of prescription errors in terms of patient harm or healthcare costs could not be established in this study. Finally, the prescription errors in our study were assessed by pharmacists only. Because it is known that the assessment of errors can differ between pharmacists and physicians, the errors should have been assessed by a physician as well. [19]

Despite these limitations, our study is the first study on the prevalence of prescription errors in older individuals with an ID and potential risk factors for these errors and we were able to investigate several risk factors, including the frailty index.

Future research should focus on the reasoning of the physician to prescribe certain drugs, handling of medication errors in daily practice and consequences of prescription errors in this specific population. Besides, the effects of interventions designed to reduce prescription errors, adverse drug events and healthcare costs should be established.

Given the results of our study we recommend physicians and pharmacists treating older individuals with an ID to be aware of potential prescription errors, especially for patients with risk factors. Besides, regular review of pharmacotherapy by a multidisciplinary group, including at least a physician and a pharmacist, is recommended to reduce medication errors.

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# 4

# Predicting adverse drug events using the number of biochemical tests as an electronic trigger

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## ABSTRACT

### Background

Adverse drug events (ADEs) in hospitalized patients might be preceded by a physician's suspicion leading to increased ordering of biochemical tests.

### Objective

To investigate whether the number of biochemical tests performed is predictive for the occurrence of ADEs in order to use it as an electronic trigger.

### Methods

During five months patients admitted to four internal medicine wards of two hospitals in the Netherlandswere included in this cohort study. The total number of biochemical tests performed per day was counted and all tests were assigned to a predefined test group. ADEs were assessed retrospectively by pharmacists. For every day of the admission patients experiencing an ADE were compared with patients without ADEs on the same day (index date). Univariate and multivariate cox-regression analyses were performed using the number of biochemical tests performed in the two days before the ADE or index date as time-dependent variable. Primary outcome was the adjusted odds ratio for the association between the total number of biochemical tests and the occurrence of ADEs. Adjusted odd ratios for the number of tests per test group were the secondary outcomes.

### Results

In this study 554 patients were included; ADEs were identified during 331 admissions (59.7%). Univariate analysis showed an association between the number of metabolic tests and the occurrence of ADEs (Hazard Ratio (HR) 1.21, 95% Confidence Interval (CI) 1.01 -1.44), but in multivariate analysis the association was not statistically significant ($HR_{adjusted}$ 1.16, 95% CI 0.97 -1.38). Neither the total number of tests nor subsets of tests (electrolytes, renal function, liver function, hematological, hemostasis or other) were statistically significantly associated with ADEs.

### Conclusion

In this study the number of biochemical tests could not be identified as a predictor for ADEs in hospitalized patients.

## INTRODUCTION

Up to sixty percent of hospitalized patients experience adverse drug events (ADEs)[1], including adverse drug reactions, which occur at doses normally used in man for treatment, prophylaxis, diagnosis or modification of physiological function[2], as well as patient harm as a result of medication errors.

Since the majority of these ADEs (88%) are not preventable[1], early detection and recognition of ADEs in daily practice is essential to limit patient harm, prolongation of hospital stay and health care expenditures and to improve patients' well-being. But unfortunately previous studies have shown that not all ADEs are recognized by the attending physician.[3-5] Therefore, automated systems using electronic triggers have been developed to support the detection of ADEs.[6, 7]

Abnormal biochemical responses (also known as drug related hazardous conditions (DRHC)[8]) are an attractive approach to detect suspected ADEs at an early stage because the temporal gap between the biochemical response and the clinical manifestation of an ADE allows health care professionals to intervene and prevent further harm.[9] Computer-based monitoring using electronic data from the hospital information system, is an example of a detection tool for this type of DRHCs .[10] For example, Kane-Gill et al. defined a list of abnormal biochemical values, known to be associated with frequently used drugs on an intensive care unit. In this study 97% of the abnormal biochemical values that were related to a drug resulted in increased monitoring or changed drug regimens to prevent further harm.[9]

Besides the use of specific laboratory values as electronic triggers, the number of biochemical tests may also be useful to detect DRHCs or ADEs at an early stage. Even when the physician did not diagnose a patient's condition yet nor actually identified an ADE, he or she may have an uneasy feeling which makes him or her concerned about a possible adverse outcome. This suspicion, also described as "gut feeling" or "sense of alarm", alerts the physician and leads to increased diagnostic procedures to clarify the patient's condition and prevent serious problems.[11-13] If this phenomenon also applies to initially subclinical or unrecognized ADEs, one may expect that the number of biochemical tests increases before an ADE is actually recognized, irrespective of the nature of the ADE. Consequently, the number of biochemical tests may be used as an electronic trigger to identify a patient at risk for ADEs before the ADE actually reveals and to target additional resources, like a multidisciplinary patient review, to these patients and improve patient safety.[14-19] Therefore, the objective of this study was to investigate whether the number of biochemical tests increases before the manifestation of ADEs with the ultimate aim to use this information as an electronic trigger.

## METHODS

### Design

This study used data of a larger prospective intervention study on the effect of a Computerized Physician Order Entry in combination with a Clinical Decision Support System for prescribing medication (CPOE/CDSS) on medication safety and associated costs.[20] The current study is designed as a cohort study that uses data that were prospectively collected after the introduction of CPOE/CDSS.

### Setting

This study was performed in two internal medicine wards (one geriatric and one general internal medicine ward) of the 600 bed teaching hospital "TweeSteden" (TSh) in Tilburg and Waalwijk and two medical wards (one general internal medicine wards divided into two units, and one gastroenterology/rheumatology ward) of the 1300 bed University Medical Center in Groningen (UMCG), the Netherlands. CPOE/CDSS was introduced on one ward at a time and on each ward the study started eight weeks after the implementation (TSh general internal medicine June 2006, TSh geriatrics April 2006, UMCG general internal medicine August 2006, gastroenterology/rheumatology January 2008).

### Patients

During five months per ward all patients admitted to the study wards for more than 24 hours were included. Patients who did not use medication during their admission were excluded from the current study. For patients that were admitted more than once during the study period, only the first admission was included to avoid the statistical complexities arising from dependence of observations. A waiver of the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of normal hospital care and routine of quality improvement and assurance. According to the Dutch Data Protection Act patients received written information about the study after which they could object to use of their medical data in this study.

### Data collection

During ward visits trained pharmacists prospectively extracted patients' characteristics (age, sex, weight and length), data on diseases (medical history, reasons for admission and diagnoses), biochemical tests performed and adverse events (i.e. untoward medical occurrences which do not need to have a causal relationship with the treatment[2]) from medical records. Medication orders issued during hospitalization were collected by reviewing CPOE/CDSS.

## Biochemical tests

During admission the total number of biochemical tests performed per day was counted. Based on known associations between abnormal biochemical values and ADEs, all performed tests were assigned to one of the following eight test groups: electrolytes (potassium, calcium, sodium, magnesium), metabolic (glucose, creatine kinase), renal function (creatinine, ureum, urine albumin), liver function (alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transpeptidase, lactate dehydrogenase, bilirubine, serum albumin), hematological (leukocytes, thrombocytes, hemoglobin, differentiation of leukocytes), hemostasis (prothrombin time, international normalized ratio, activated partial thromboplastin time), therapeutic drug monitoring (serum drug levels) or other (all other biochemical tests).[3, 9, 21-23] Subsequently, the number of performed tests per test group per day was calculated.

## Adverse drug events

Adverse drug events include adverse drug reactions and patient harm resulting from medication errors (i.e. preventable adverse drug events) occurring during hospitalization. To determine adverse drug reactions (ADRs), the causal relation between all recorded adverse events and any drug taken by the patient was assessed by two pharmacists after the data collection period. Consensus was evaluated using the first three items of the Yale algorithm, also known as the Kramer scale[24]: knowledge about the relation between the drug and the event, the presence of underlying clinical conditions which could be responsible for the event (using the collected data on diseases and diagnoses) and the timing of the event, as we previously described in detail.[1] Following this algorithm, the causal relationship between an event and a drug could be defined as unlikely (score $< 0$), possible (score $\geq 0$ and $\leq 3$) or probable (score $= 4$). Only events with a possible or probable relationship with drug treatment were included in the analysis.

Preventable adverse drug events (pADEs) were defined as adverse drug events with a possible or probable causal relationship with a medication error. This causal relationship was assessed in consensus between five pharmacists following the same Yale algorithm

All ADEs were classified according to the WHO Adverse Reaction Terminology on the level of system organ class.[2] Critical terms, defined as "events referring to, or possibly being indicative for, serious disease states, which have been regarded as particularly important to follow up"[2], were marked.

## Statistical analysis

Patients' age was categorized based on the quartiles of our population. Reason for admission was classified according to the International Classification of Diseases ICD-10.[25] Length of stay was calculated and for every single day of a patient's admission the number

of drugs was counted separately. Drugs used at the first day of admission were categorized according to Anatomical Therapeutic Chemical (ATC) classification system.

Patients were included in the analysis until the occurrence of an ADE, discharge from hospital or death, whichever occurred first. For every day of the admission patients experiencing an ADE on that specific day were compared with patients without ADEs on the same day (index date) using Cox-regression analysis. Using this predictive model, data beyond the index date may not be used in the analysis, meaning that a patient that experienced an ADE after this day is considered a control until the ADE occurred. For example, a patient who experienced an ADE on the fifth day of admission was included in the analysis as a control on day one to four.

Univariate Cox-regression analysis was performed using the total number of biochemical tests carried out in the two days before the ADE or index date as time-dependent variable. For patients with an ADE on the second day of the admission and their controls only the number of tests of the first day of admission, including tests performed in the emergency room, was included. Patients experiencing an ADE on the first day of admission were excluded from the analysis.

Sub analyses were performed for the number of tests per test group. Variables that were associated with ADEs in a previous analysis of our study data were included as potential confounders: gender, age (categorized into quartiles), ward and number of drugs.[1] Because the Cox-regression analysis uses longitudinal data, the number of drugs, which can change during admission, is counted for every day of the admission separately and included in the analysis as a continuous variable, both for patients with ADEs and patients without ADEs. Crude hazard ratios with 95% confidence intervals were calculated.

In the multivariate Cox-regression analysis potential confounders that were statistically significantly associated with the occurrence of ADEs in the univariate analysis ($p<0.05$) were entered into a multivariate model to calculate adjusted hazard ratios with 95% confidence intervals. The assumption of proportional hazards in the multivariate Cox-regression models was verified by studying the associations of the effect of each variable regarding the relation with time, i.e. by including interaction terms with time (day of admission) in the Cox regression models. A sample size was not calculated, as the expected effect size could not be estimated due to the lack of previous studies on this subject.

All statistical analyses were performed using SPSS version 21 (IBM Software).

## RESULTS

During the study period 603 patients were admitted to the study wards, of which 16 patients were excluded because they did not use any medication during admission. Four

other patients were excluded due to missing data (biochemical laboratory results or date of adverse drug event) and 29 readmissions were excluded. None of the patients objected to use of their data for this study. In total 554 patients were included in our analysis. Characteristics of the included patients and admissions are presented in table 1.

**Table 1:** Characteristics of patients (n=554)

| Patient characteristics | Patients with ADEs n=331 n (%) | Patients without ADEs n=223 n (%) | All patients (n=554) n (%) |
|---|---|---|---|
| Age, years (median, range) | 77 (16-100) | 61 (17-96) | 71 (16-100) |
| Female gender | 203 (61.3) | 112 (50.2) | 315 (56.9) |
| Reason for admission (ICD10) | | | |
| Diseases of the digestive system (K) | 60 (18.1) | 76 (34.1) | 136 (24.5) |
| Diseases of the circulatory system (I) | 39 (11.8) | 10 (4.5) | 49 (8.8) |
| Symptoms, signs and abnormal clinical and laboratory findings (R) | 32 (9.7) | 16 (7.2) | 48 (8.7) |
| Neoplasms (C) | 21 (6.3) | 23 (10.3) | 44 (7.9) |
| Endocrine, nutritional and metabolic diseases (E) | 20 (6.0) | 18 (8.1) | 38 (6.9) |
| Diseases of the genitourinary system (N) | 27 (8.2) | 9 (4.0) | 36 (6.5) |
| Other | 108 (32.6) | 55 (24.7) | 163 (29.4) |
| Unknown | 24 (7.3) | 16 (7.2) | 40 (7.2) |
| Length of stay (median, range) | 14 (3-100) | 6 (1-38) | 10 (1-100) |
| Ward | | | |
| 1 | 78 (23.6) | 122 (54.7) | 200 (36.1) |
| 2 | 100 (30.2) | 51 (22.9) | 151 (27.3) |
| 3 | 120 (36.3) | 11 (4.9) | 131 (23.6) |
| 4 | 33 (10.0) | 39 (17.5) | 72 (13.0) |
| Number of drugs at admission (median, range) | 6 (0-22) | 4 (0-17) | 5 (0-22) |
| Use of therapeutic group, according to ATC[a] | | | |
| Alimentary tract and metabolism (A) | 218 (65.9) | 138 (61.8) | 356 (64.3) |
| Blood and blood forming organs (B) | 190 (75.4) | 90 (40.4) | 280 (50.5) |
| Cardiovascular system (C) | 180 (54.4) | 94 (42.2) | 274 (49.5) |
| Systemic hormonal preparations (H) | 77 (23.3) | 40 (17.9) | 117 (21.1) |
| Anti-infectives for systemic use (J) | 89 (26.9) | 53 (23.8) | 142 (25.6) |
| Musculo-skeletal system (M) | 50 (15.1) | 39 (17.5) | 89 (16.1) |
| Nervous system (N) | 180 (54.3) | 86 (38.9) | 266 (48.9) |
| Respiratory system (R) | 59 (17.8) | 27 (12.1) | 86 (15.5) |
| Other (D,G,L,P,S,V and unknown)[b] | 95 (28.7) | 56 (25.1) | 151 (27.3) |

ICD10= International Classification of Diseases; ATC= Anatomical Therapeutic Chemical (ATC) classification system

[a] number of patients that used one or more drugs from the specific class at admission

[b] D= Dermatologicals, G= Genito-urinary system and sex hormones, L= Antineoplastic and immunomodulating agents, P= Antiparasitic products, insecticides and repellents, S= Sensory organs, V= Various

Adverse drug events were identified during 331 admissions (59.7%) and 18 (5.4%) of these events were considered preventable adverse drug events. Details of the identified ADEs are presented in table 2. Gastro-intestinal disorders (29.3%), psychiatric disorders

**Table 2:** Details of identified adverse drug events (n=331)

| Details of adverse drug events | Adverse drug reactions n = 313 n (%) | Preventable adverse drug events n = 18 n (%) | Total n = 331 n (%) |
|---|---|---|---|
| Nature of event, according to system-organ class | | | |
| Gastro-intestinal system disorders | 92 (29.4) | 5 (27.8) | 97 (29.3) |
| Psychiatric disorders | 46 (14.7) | 1 (5.6) | 47 (14.2) |
| Nervous system disorders | 38 (12.1) | 1 (5.6) | 39 (11.8) |
| Respiratory system disorders | 24 (7.7) | - - | 24 (7.3) |
| Metabolic and nutritional disorders | 14 (4.5) | 2 (11.1) | 16 (4.8) |
| Cardiovascular disorders | 15 (4.8) | 1 (5.6) | 16 (4.8) |
| Other | 84 (26.8) | 8 (44.4) | 92 (27.8) |
| Critical adverse drug events | 35 (11.2) | 5 (27.8) | 40 (12.1) |
| Hypoglycaemia | 5 | | 5 |
| International normalised ratio increased | 3 | 2 | 5 |
| Hypertension | 4 | | 4 |
| Phlebitis | 4 | | 4 |
| Coagulation time increased | 2 | | 2 |
| Collaps | 2 | | 2 |
| Hallucinations | 2 | | 2 |
| Hyperkalaemia | 1 | 1 | 2 |
| Melaena | 2 | | 2 |
| Pulse abnormal | 2 | | 2 |
| Other[a] | 8 | 2 | 10 |
| Pharmacotherapeutic group related to ADE, according to ATC classification | | | |
| Alimentary tract and metabolism (A) | 56 (17.9) | 2 (11.1) | 58 (17.5) |
| Blood and blood forming organs (B) | 19 (6.1) | 5 (27.8) | 24 (7.3) |
| Cardiovascular system (C) | 76 (24.3) | 4 (22.2) | 80 (24.2) |
| Systemic hormonal preparations (H) | 16 (5.1) | - - | 16 (4.8) |
| Anti-infectives for systemic use (J) | 27 (8.6) | 2 (11.1) | 29 (8.8) |
| Musculo-skeletal system (M) | 7 (2.2) | 2 (11.1) | 9 (2.7) |
| Nervous system (N) | 96 (30.7) | 3 (16.7) | 99 (29.9) |
| Respiratory system (R) | 12 (3.8) | - - | 12 (3.6) |
| Other (G,L,S)[b] | 4 (1.3) | - - | 4 (1.2) |

ATC= Anatomical Therapeutic Chemical (ATC) classification system

[a] Other critical adverse drug events include cheyne stokes respiration, delirium, epistaxis, hypokalemia, international normalized ratio decreased, leucopenia, renal function abnormal, restless legs, stridor, wheezes

[b] G= Genito-urinary system and sex hormones, L= Antineoplastic and immunomodulating agents, S= Sensory organs

(14.2%) and nervous system disorders (11.8%) were the most common ADEs. 40 ADEs were defined as critical terms, including hypoglycaemia, increased international normalized ratio, phlebitis and hyperkalaemia.

Median time to occurrence of the ADE was 3 days (range 1-21 days). The risk of an ADE was highest on day 2 and decreased with increased length of stay after day 2 (figure 1).

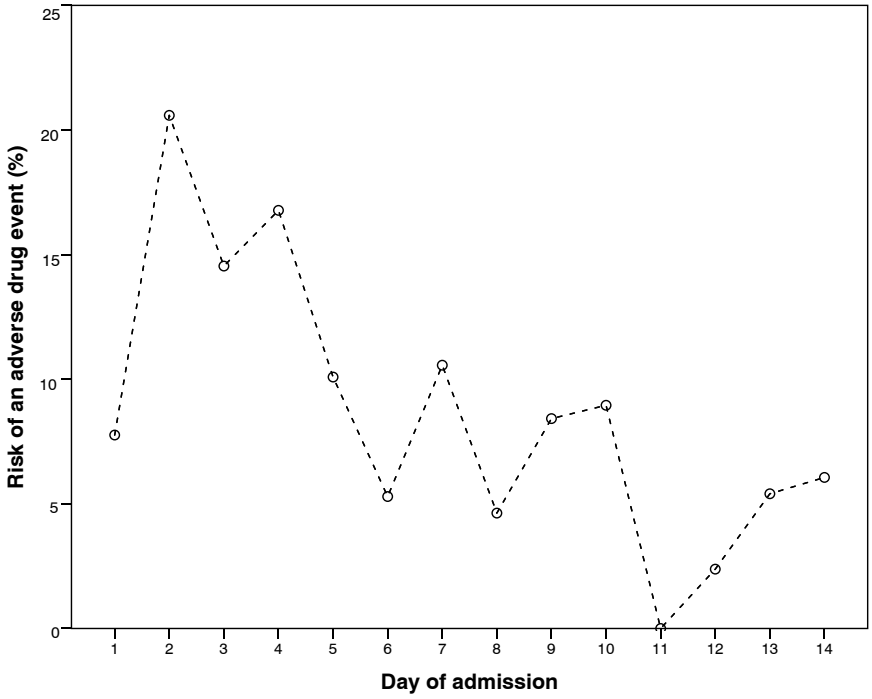


**Figure 1:** Graph showing the risk of an adverse drug event for each day of admission

The numbers of patients at risk at the various days are shown at the bottom. After day 14 only 4 of the remaining patients had an ADE (during a total of 147 patient admission days after day 14).

The prior number of tests according to admission day and whether or not an ADE had occurred is shown in figure 2. This figure shows that patients with and without an ADE do not consistently differ with respect to the prior total number of biochemical tests.

Univariate regression analysis of potential important factors regarding the occurrence of adverse drug events showed significant relations with gender ($p=0.006$), age ($p<0.001$) and the number of drugs ($p<0.001$). There were also significant differences between the four wards studied ($p<0.001$). Therefore, in all evaluations of the number of biochemical tests the analyses were adjusted for gender, age, ward and the number of drugs.

Univariate Cox-regression analysis of the occurrence of an ADE and the total number of biochemical tests showed no significant relation (Hazard Ratio (HR) 1.00; $p=0.506$).

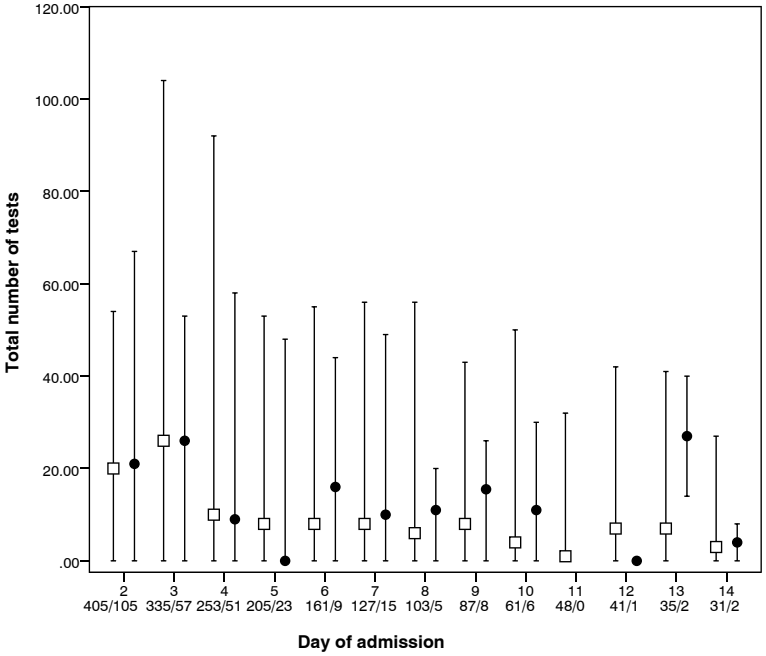


**Figure 2:** Prior number of biochemical tests performed for patients with and without an adverse drug event (ADE) for admission day 2 to 14

At each day of admission the median value of the total number during the two days before the indicated day is shown according to whether or not an ADE had occurred at the day indicated (closed circles: ADE, open squares: no ADE). The bars represent the ranges. The numbers below the horizontal axis at each day of admission represent the numbers of patients at risk without an ADE at the indicated day / number of cases with an incident ADE at the indicated day.

To further clarify the figure, at admission day 8 for example, there were 108 patients still at risk for an ADE. Five of these patients developed an ADE at this particular day, and 103 did not. For these two groups the median values of the total number of tests during the preceding two days (days 6 and 7) was 11 and 6, respectively.

Also in multivariate analysis no significant relation was found. The adjusted hazard ratio associated with an increase of one additional test was 1.01 (95% Confidence Interval (CI): 1.00-1.01; p=0.258), see table 3.

Results of the univariate and multivariate Cox-regression analyses for the numbers of biochemical tests grouped according to type of test are presented in table 4. In univariate analysis only the number of metabolic tests showed an association with the occurrence of ADEs (HR 1.21, 95% CI 1.01-1.44, p=0.037, meaning that for every additional metabolic test performed, the risk of an ADE increases with 21%). However, after correction for gender age, number of drugs and ward in the multivariate analysis, the significance of the association was lost ($HR_{adjusted}$ 1.16, 95% CI 0.97 -1.38, p=0.112).

**Table 3:** Results of multivariate Cox regression analysis regarding the incidence rate of adverse drug events according to various factors

| Variable | Hazard ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| Total nr of biochemical tests | 1.01[a] | 1.00-1.01 | 0.258 |
| Gender | 1.20 | 0.94-1.53 | 0.152 |
| Age category | | | 0.021[b] |
| ≤ 52 yrs (n=137) | reference | - | - |
| 53-70 yrs (n=135) | 0.83 | 0.57-1.23 | 0.353 |
| 71-81 yrs (n=143) | 0.87 | 0.59-1.28 | 0.478 |
| ≥82 yrs (n=139) | 1.34 | 0.90-1.98 | 0.145 |
| Number of drugs | 1.10[c] | 1.07-1.13 | <0.001 |
| Ward[d] | | | <0.001[b] |
| 1 (n=200) | reference | - | - |
| 2 (n=151) | 1.89 | 1.35-2.66 | <0.001 |
| 3 (n=131) | 2.47 | 1.72-3.55 | <0.001 |
| 4 (n=72) | 0.88 | 0.57-1.36 | 0.566 |

[a]Effect per additional test
[b]Overall p-values
[c]Effect per additional drug
[d]Wards are ranked according to the number of patients

**Table 4:** Associations between number of biochemical tests and adverse drug events after univariate (hazard ratio) and multivariate (adjusted hazard ratio) cox regression analysis

| Number of biochemical tests | Hazard ratio (CI95) | p | Hazard ratio$_{adj}$ (CI95) | p-value |
|---|---|---|---|---|
| Number of tests per test group | | | | |
| Electrolytes | 1.02 (0.95 - 1.08) | 0.642 | 1.04 (0.96 - 1.11)[c] | 0.347 |
| Metabolic | 1.21 (1.01 - 1.44)[a,b] | 0.037 | 1.16 (0.97 - 1.38)[c] | 0.112 |
| Renal function | 1.04 (0.95 - 1.13) | 0.435 | 1.05 (0.96 - 1.16)[c] | 0.277 |
| Liver function | 0.99 (0.96 - 1.02) | 0.567 | 1.03 (1.00 - 1.07)[c] | 0.085 |
| Hematology | 0.99 (0.94 - 1.05) | 0.766 | 1.02 (0.96 - 1.08)[c] | 0.538 |
| Hemostasis | 0.91 (0.76 - 1.08) | 0.286 | 0.99 (0.83 - 1.18)[c] | 0.916 |
| Therapeutic drug monitoring | 1.14 (0.66 - 1.96) | 0.647 | 0.90 (0.51 - 1.57)[c] | 0.703 |
| Other | 1.01 (1.00 - 1.02) | | 1.00 (0.99 - 1.02)[c] | 0.552 |

CI95 = 95% confidence interval, HRadj = adjusted hazard ratio
[a] statistically significant (p<0.05)
[b] The risk of an adverse drug event increases with 21 % for every additional metabolic test performed.
[c] Adjusted for gender, age, number of drugs, and ward.

## DISCUSSION

Our study shows that the number of biochemical tests is not higher for hospitalized patients with an ADE than for patients without an ADE in the 2 days prior to the ADE.

In univariate analysis a larger number of metabolic tests showed an increased risk of ADEs. Metabolic tests include glucose and creatine kinase measurements. Disturbances of serum glucose levels are frequently caused by drugs such as corticosteroids or blood glucose lowering drugs. To diagnose these ADEs measurement of serum glucose is performed. Therefore patients whose serum glucose is frequently measured may be patients at risk of hyperglycaemia or hypoglycaemia. The same argumentation holds for creatine kinase, which is often determined when myopathy is suspected if patients use a statin. However, the significance of the relation was lost in multivariate analysis.

The most common ADEs in this cohort were relatively mild gastro-intestinal disorders, psychiatric disorders and nervous system disorders. These ADEs do not have a clear relation with certain biochemical values and are not diagnosed or evaluated by biochemical values. This may partly explain why we did not find an association between the number of tests and ADEs, irrespective of their nature. More serious ADEs for which we expected an association with biochemical values, such as renal failure, liver failure or blood cell disorders, were uncommon in our population. Due to the low prevalence of events per class of ADE, associations between number of tests and specific classes of ADEs could not be assessed.

In addition, in our cohort the median time to occurrence of an ADE after admission was relatively short. This corresponds with previous results of Hurwitz et al. who showed that the occurrence of ADRs is highest during the first or first two days of hospital admission.[19] These ADRs could be related to starting new drugs at admission, which is a risk factor for ADRs.[17]

During the first days of an admission the mean number of tests performed was also higher in our study, probably to clarify the patient's condition. These tests may have outnumbered the biochemical tests that were requested as a result of the physician's suspicion. Besides, the number of tests performed can vary between different physicians, according to their specialty or experience. In the studied hospitals (a teaching hospital and a university hospital) mainly residents are responsible for test ordering in the studied hospitals (a teaching hospital and a university hospital), which may result in inappropriate and avoidable test requests, especially by junior trainees.[26] This phenomenon might have influenced our results as well.

The analysis in this study was based on the assumption that a physician will have a suspicion one or two days before an ADE becomes manifest. However, the number of tests could also be argued to increase immediately after an ADE appears. If future research should confirm this increase and its predictive value, electronic monitoring of the number

of tests may be useful to identify patients that experience an ADE at an early stage in order to prevent further harm.

This study has three main limitations. First, ADEs were assessed retrospectively based on physicians' notes and nurses' notes. Therefore, it is possible that the physician did not have any suspicion and as a consequence did not perform additional diagnostic procedures. Second, the results of the biochemical tests were not taken into account in this study, whereas previous studies have shown that abnormal biochemical values can be used as a predictor to identify patients at risk of an ADE.[3, 9, 27] Third, we could not discriminate between ADEs and other possible cause of increases of biochemical tests, such as worsening of underlying conditions or the manifestation of other conditions, such as nosocomial infections. In addition, data on comorbid conditions nor severity of the disease state were taken into account in this study. Unfortunately, we were not able to include any of these potential confounders in our longitudinal analysis. However, because we did not find an association between the number of tests and the occurrence of ADEs, correction for these confounders would be unlikely to affect our results or conclusion.

This study is the first study on a potential association between the number of biochemical tests and ADEs. Because we found no significant associations between the number of performed biochemical tests and the occurrence of ADEs the total number of biochemical tests cannot be used for computerized detection of hospitalized patients that may develop an ADE. However, some other options to use the number of tests as an electronic trigger should be explored. For example, the relation between specific types of tests and more serious types of ADEs, changes in trends of ordering tests for each patient with a suspected ADE, and the possible increase of performed tests immediately after an ADE is identified should be studied, taking into account other reasons for increases in biochemical tests.

To conclude, in this study the number of biochemical tests could not be identified as a predictor for ADEs in hospitalized patients. Automated detection of adverse drug events at an early stage should thus be focused on other parameters.

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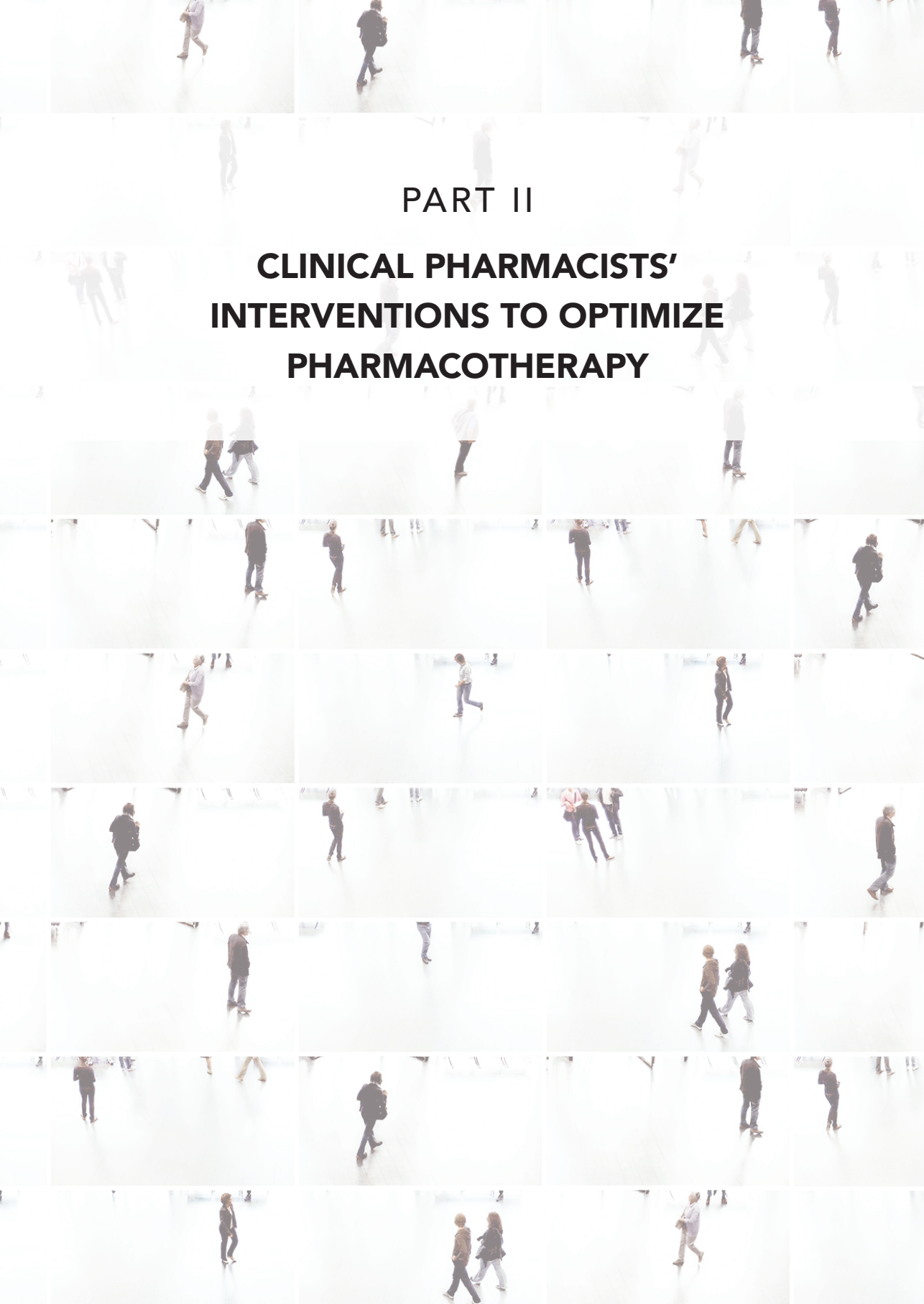

# PART II

# CLINICAL PHARMACISTS' INTERVENTIONS TO OPTIMIZE PHARMACOTHERAPY

# 5

# Identification of drug-related problems by a clinical pharmacist in addition to computerized alerts

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## ABSTRACT

### Background

Both clinical pharmacists and computerized physician order entry systems with clinical decision support (CPOE/CDSS) can reduce drug-related problems (DRPs). However, the contribution of a clinical pharmacist in addition to CPOE/CDSS has not been established in a prospective study.

### Objective

To determine which DRPs can be identified by a clinical pharmacist in a setting with routine use of CPOE/CDSS.

### Methods

In this observational prospective follow-up study a clinical pharmacist reviewed the pharmacotherapy of patients admitted to surgical and neurological wards in a teaching hospital in the Netherlands to identify DRPs (i.e. medication errors and adverse drug events) and discussed the relevance of identified problems and interventions to resolve these with the responsible physician. Acceptance of the proposed interventions and the presence of alerts in CPOE/CDSS were assessed. Primary outcome was the proportion of DRPs identified by the clinical pharmacist that also triggered a CPOE/CDSS alert. Differences between the DRPs that generated an alert and those that did not were expressed as relative risks or analyzed with Chi square statistics or Mann–Whitney U tests. Primary outcome was the proportion of drug-related problems identified by the clinical pharmacist that also generated an alert in the CPOE/CDSS.

### Results

During 1206 medication reviews, 442 potential DRPs were identified; 286 (65%) DRPs were considered relevant and 247 (56%) of the proposed interventions were accepted. A CPOE/CDSS alert was generated for 35 (8%) of the DRPs the clinical pharmacist identified. The only difference between problems that triggered an alert and those that did not was the class of the DRP (indication 23% vs. 36%, effectiveness 23% vs. 13%, safety 23% vs. 10% and pharmaceutical care issues 31% vs. 42%, $p = 0.02$). CPOE/CDSS triggered 623 additional alerts that were handled during routine pharmacy service.

### Conclusions

As most DRPs identified by a clinical pharmacist were not detected in daily clinical practice by CPOE/CDSS, a clinical pharmacist contributes to reducing DRPs. The sensitivity of CPOE/CDSS to detect certain classes of problems should be optimized.

## INTRODUCTION

Problems associated with pharmacotherapy, including adverse drug events and medication errors, occur frequently in hospitalized patients.[1-3] Since the report "To err is human" showed the impact of these drug-related problems on morbidity, mortality, and health-care expenditures more than a decade ago, improving medication safety has become an important goal for health care professionals.[3] However, even in hospitals with a heavy programmatic focus on safety, adverse drug events still occur in a considerable proportion of admitted patients.[4, 5]

Organizational factors (such as local workflows; procedures regarding ordering, dispensing, and administration of medication; and knowledge and training of personnel) have been associated with the occurrence of drug-related problems.[2, 6-11] One of such organizational factors, namely use of health information technologies, can contribute to a reduction of these drug-related problems.[6, 12] This has been shown for computerized physician order entry in combination with a clinical decision support system (CPOE/CDSS). The basic CPOE/CDSS used in the Netherlands is mainly effective in preventing medication errors, particularly administrative prescribing errors (such as incomplete or illegible orders), dosing errors and transcription errors and has a high sensitivity for identifying drug-drug interactions.[6, 13-20] However, basic CPOE/CDSS is not able to detect all pharmacotherapeutic errors, which are more likely to result in adverse drug events,[20, 21] and generates a substantial amount of alerts that are not clinically relevant, resulting in alert fatigue.[19, 22]

Clinical pharmacists can combine current diagnoses, laboratory values, medical history, and prescribing guidelines with the current pharmacotherapy of a patient. As a result a clinical pharmacist could possibly detect more therapeutic errors and adverse drug events than CPOE/CDSS. Although active participation of clinical pharmacists on the ward has been shown to improve medication safety,[23-32] the contribution of a clinical pharmacist in addition to CPOE/CDSS has not yet been established in a prospective study.

This study was designed to determine which drug-related problems can be identified by a clinical pharmacist in a setting with routine use of CPOE/CDSS and whether problems that were also identified by CPOE/CDSS differed from those that were only identified by the clinical pharmacist.

## METHODS

### Design and setting

We performed an observational prospective follow-up study from November 2009 to July 2010 on two surgical and two neurological wards in St. Elisabeth hospital, a 600-bed teaching hospital in Tilburg, the Netherlands. We selected surgical wards for this study, because surgical patients have been shown to be at risk of drug-related problems.[33, 34] The neurological wards were selected to compare surgical wards with medical wards.

In this hospital the process of medication ordering and administration consists of a system for computerized physician order entry and barcode-assisted medication administration (Theriak Medication Management®, Theriak ehf, Tilburg, The Netherlands). The integrated basic clinical decision support system, based on the Dutch national drug database G-standard® (Z-Index, The Hague, The Netherlands), generates intrusive alerts (pop-ups) for overdosing, duplicate therapy, and allergies at the time of prescribing.[35] Drug-drug interactions are always visible for the physician during and after prescribing, but these do not trigger intrusive alerts during prescribing to prevent alert fatigue.[22] Routine central pharmacy service consisted of on-call duty for consultations and central handling of drug-drug interactions and overridden CPOE/CDSS alerts by pharmacy technicians and pharmacists. Alerts are primarily assessed by pharmacy technicians following local procedures as part of their daily routine. They can accept alerts that are not clinically relevant for the individual patient (for example drug-drug interactions considering preadmission pharmacotherapy or dosage alerts for dosages that are according to guidelines or handbooks), send an information leaflet to the ward (for example to advise additional monitoring) or submit the alert to a pharmacist.

### Patients

Patients included in this analysis had at least one potential drug-related problem (as assessed by the clinical pharmacist). This study fell within the boundaries of normal hospital care and routine of quality improvement and therefore did not need Medical Ethics approval in the Netherlands.

### Drug-related problems

Drug-related problems were defined as circumstances that involve a patient's drug treatment that actually or potentially interfere with the achievement of an optimal outcome. These include medication errors (defined as any error in the process of prescribing, dispensing or administering a drug, whether there are adverse consequences or not) as well as adverse drug events (defined as any injury related to the use of a drug).[9, 36] The classification of drug-related problems (table 1) is derived from the classification recently described in detail by Leendertse et al.[37] which was based on the work of Strand et al..[38]

**Table 1:** Classification of drug-related problems and pharmaceutical care issues

| Class | Drug-related problem | Definition | Example |
|---|---|---|---|
| Indication | Additional drug therapy required | The patient has a medical condition or is experiencing symptoms that require the initiation of new or additional drug therapy or is at high-risk of developing a new medical condition for which additional drug therapy is indicated. | - Laxative indicated during opioid use (severity E) |
| | Unnecessary drug therapy | The patient is undergoing drug therapy that is unnecessary given his or her present condition. | - Continuation of treatment with acetazolamide (initiated in intensive care unit) without clear indication (severity E) |
| Effectiveness | Ineffective drug therapy | The drug is not being effective at producing the desired response. The patient is not experiencing the intended positive outcome from a certain regimen, or the intended outcome is not reached. Or an alternative drug therapy has a higher probability of producing the desired outcome. | - Butylscopolamine suppositories for abdominal spasms (absorption after rectal administration is less than 3%) (severity C) |
| | Dosage too low | The patient has a medical condition for which too little of the correct drug is being taken to produce the desired beneficial outcome, or the patient is at risk of developing a new medical condition because too little of the correct drug is being taken to expect a beneficial outcome. The patient's drug concentration in the body can be below the desired therapeutic range, or the timing of prophylaxis can be inadequate for the patient. Or, dose, interval and duration can be inadequate for the patient, or drug, dose, route or formulation conversions were inadequate for the patient. | - Prophylactic dose of low molecular weight heparin prescribed instead of therapeutic dose for atrial fibrillation during temporary cessation of oral anticoagulants (severity G) |
| Safety | Adverse drug event | The patient has a medical condition, or is experiencing symptoms, or is at risk of developing a medical condition which is an undesired effect and is related to the drug therapy. This can be an idiosyncratic reaction to the drug, an allergic reaction to the drug, or a pharmacologically expected reaction to the drug, possibly due to a medication error. | - Use of oxybutynin could have contributed to delirium (severity E) |
| | Dosage too high | The patient has a medical condition for which too much of the correct drug is being taken, or the patient is at risk of developing a new medical condition because too much of the correct drug is being taken. The patient's drug concentration in the body can be above the desired therapeutic range, or the drug dose can be escalating too rapidly, or there can be drug accumulation from chronic administration or dose, interval, and duration can be inadequate for the patient, or drug, dose, route or formulation conversions were inadequate for the patient. | - Colchicine 0.5 mg every 8 hours for a patient with a glomerular filtration rate of 22 ml/min. Recommended dose given this glomerular filtration rate is 0.5 mg every 12 hours (severity F) |
| Drug use | Drug use problem | The patient is unable or unwilling to take a drug regimen that a health care provider has clinically judged to be appropriately indicated, adequately efficacious and able to produce the intended outcomes without any undesired effects, or drug therapy is not optimally convenient. | - Use of amlodipine 5 mg twice daily; 10 mg once daily would be more convenient for the patient (severity A) |
| Pharmaceutical Care | Monitoring | An intermittent series of observations in time, carried out to determine the effectiveness, safety, and adherence to drug therapy. | - Monitor digoxin serum levels for a patient with a decreased renal function (severity D) |
| | Drug-drug interaction | A combination of two or more drugs administered to one patient that can result in a modification of the effect of at least one drug. | - Folic acid once weekly and methotrexate once weekly prescribed on the same day, while administration on the same day is contra-indicated (severity E) |
| | Contra-indicated drug | A drug that is undesired because of the medical condition of the patient. | - Prescription for codeine, while it was explicitly contra-indicated due to somnolence (severity E) |
| | Lifestyle | The lifestyle of the patient that could interfere with effective and safe drug therapy, or that could result in non-adherence. | - Did not occur in current study |
| | Duplicate therapy | The use of two or more drugs with the same ATC classification* and/or with similar pharmacodynamic properties, which can lead to adverse drug events. | - Combination of low dose aspirin and coumarin without indication for combination (severity G) |
| | Discrepancy with pre-admission pharmacotherapy | Unintended discrepancy between pre-admission pharmacotherapy and in-hospital treatment, including unintended discontinuation of a pre-admission drug therapy. | - Unintended discontinuation of latanoprost eye drops for glaucoma at admission (severity E) |

Based on Leendertse et al.[37] and Strand et al.[38]

ATC classification = Anatomical Therapeutic Chemical (ATC) classification system

Because discrepancies can occur between pre-admission pharmacotherapy and in-hospital treatment, this problem was added to the classification.[39]

## Data collection

To identify drug-related problems that required an intervention, a clinical pharmacist reviewed pharmacotherapy of all patients in the study wards weekly, on a set day, until discharge of the patients. Current medical diagnoses, laboratory results, medical history and medication history were taken into account.

For each patient, the relevance of identified potential drug-related problems and proposed interventions to ameliorate them were discussed with the attending physician. Subsequently, the clinical pharmacist assessed the acceptance of the proposed interventions for relevant drug-related problems, as well as the presence and pharmacy handling of alerts in the CPOE/CDSS. Additionally, the number and type of CPOE/CDSS alerts for reviewed medication orders of included patients that were handled by routine central pharmacy service were extracted from CPOE/CDSS.

Patients' characteristics (age and sex) and relevant medical data (reason for admission, medical history, and laboratory results) were extracted from medical records.

## Severity of drug-related problems

The index of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), which had been designed to classify medication errors into nine classes based on severity of related patient outcomes, was adapted to assess the severity of all drug-related problems in terms of their potential to cause patient harm had they not been averted (table 2).[40] Each problem was retrospectively assessed separately by two hospital pharmacists/ clinical pharmacologists and one medical specialist (a surgeon for surgical cases and a neurologist for neurological cases). Consequently, the three raters reached consensus on severity for all cases. [41]

## Outcomes

Primary outcome was the proportion of drug-related problems identified by the clinical pharmacist that also generated an alert in the CPOE/CDSS. Secondary outcomes were the differences between drug-related problems that were detected by the clinical pharmacist only and drug-related problems that also generated an alert in the CPOE/CDSS. The differences looked for were the class, severity, relevance and acceptance of proposed interventions as well as patient characteristics (gender, age, number of drugs during admission and number of drugs at time of medication review, medical specialty, and length of stay on study ward).

**Table 2:** Severity categories for drug-related problems

| Category | | Content |
|---|---|---|
| A | Non-relevant problem | A drug-related problem that is not relevant for the given patient |
| B | Relevant problem, no patient harm | A drug-related problem that will not reach the patient |
| C | | A drug-related problem occurred that may reach the patient but will not cause patient harm |
| D | | A drug-related problem that may reach the patient and will require monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm |
| E | Relevant problem, patient harm | A drug-related problem that may contribute to or result in temporary harm to the patient and required intervention |
| F | | A drug-related problem that may contribute to or result in temporary harm to the patient and may require initial or prolonged hospitalization |
| G | | A drug-related problem that may contribute to or result in permanent patient harm |
| H | | A drug-related problem that may require intervention necessary to sustain life |
| I | | A drug-related problem that may contribute to or result in the patient's death |

Reference: National Coordinating Council for Medication Error Preventing and Reporting. NCC MERP Index for Categorizing Medication Errors.[40]

In order to describe the routine pharmacy service for the included patients, the number and type of CPOE/CDSS alerts handled by the central pharmacy service that were not identified or not considered relevant by the clinical pharmacist are also described.

## Data analysis

All data were analyzed with SPSS version 17.0. To identify differences between drug-related problems that were detected only by the clinical pharmacist and those that were also detected by CPOE/CDSS chi-square tests were performed for categorical nominal variables. Continuous variables were analyzed with Mann–Whitney U tests. A p-value less than 0.05 was considered statistically significant for both tests.

## Results

The clinical pharmacist performed 1206 medication reviews and detected at least one drug-related problems during 276 reviews. In total 442 possible drug-related problems were identified concerning 251 admissions of 228 patients (17 patients were admitted at least twice). Of the identified problems 286 (65%) problems were deemed relevant for the individual patient and 247 (56%) of the 442 proposed interventions were accepted by the physicians. Among the 195 (44%) rejected interventions were those proposed for problems that were not relevant according to the physician (n=156). Besides, 39 interven-

tions for relevant problems were rejected, mainly because the patient had already been discharged or would be discharged soon (n=9) or because the drug therapy had been initiated by another specialist (n=8).

Examples of identified drug-related problems and their severity are presented in table 1. Of the 442 possible drug-related problems identified by the clinical pharmacist, 35 (8%) problems generated a CPOE/CDSS alert. Details on patient characteristics, relevance of drug-related problems and the acceptance of interventions are presented in figure 1.

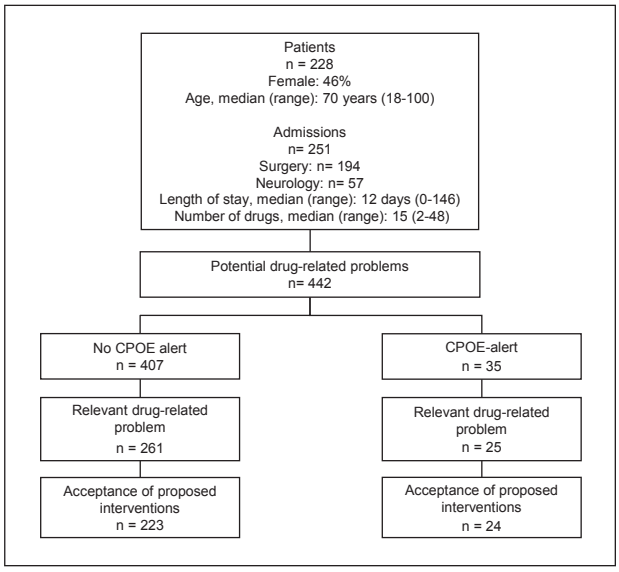


**Figure 1:** Patient characteristics and drug-related problems

Table 3 shows the frequency of different classes of identified drug-related problems. The most common drug-related problems identified by the clinical pharmacist were unnecessary drug therapy (21%), requirement of additional drug therapy (14%) and discrepancy with pre-admission pharmacotherapy (14%).

Table 4 presents the characteristics of drug-related problems detected by the clinical pharmacist only and problems that also triggered an alert. There was a significant difference between the classes of drug-related problems that were detected by the clinical pharmacist only and the classes of problems that also generated a CPOE/CDSS alert (p=0.02). Problems concerning indication (36% versus 23%) and pharmaceutical care issues (42% versus 31%) were more frequently identified by the clinical pharmacist only. Problems regarding effectiveness (23% versus 13%) or safety issues (23% versus 10%) generated a CPOE/CDSS alert more often. The severity, proportion of relevant problems, acceptance

**Table 3:** Frequency of classes of identified drug-related problems

| Class | Subclass of drug-related problem | Problems detected by: Clinical pharmacist only n=407 n (%) | Problems detected by: Clinical pharmacist and CPOE n=35 n (%) | Total n=442 n (%) |
|---|---|---|---|---|
| Indication | Additional drug therapy required | 54 (13) | 7 (20) | 61 (14) |
| | Unnecessary drug therapy | 91 (22) | 1 (3) | 92 (21) |
| Effectiveness | Ineffective drug therapy | 9 (2) | 2 (6) | 11 (3) |
| | Dosage too low | 44 (11) | 6 (17) | 50 (11) |
| Safety | Adverse drug event | 16 (4) | 3 (9) | 19 (4) |
| | Dosage too high | 23 (6) | 5 (14) | 28 (6) |
| Drug use | Drug use problem | 16 (4) | 3 (9) | 19 (4) |
| Pharmaceutical Care | Monitoring | 34 (8) | 0 (0) | 34 (7) |
| | Drug-drug interaction | 3 (1) | 2 (6) | 5 (1) |
| | Contra-indicated drug | 5 (1) | 1 (3) | 6 (1) |
| | Lifestyle | 0 (0) | 0 (0) | 0 (0) |
| | Duplicate therapy | 52 (13) | 2 (6) | 54 (12) |
| | Discrepancy with pre-admission pharmacotherapy | 60 (15) | 3 (9) | 63 (14) |

of proposed interventions, and patient characteristics did not significantly differ between drug-related problems that did generate a CPOE/CDSS alert and those that did not.

During routine pharmacy service, CPOE/CDSS generated 623 alerts for actual medication orders of included patients that were not identified or not considered relevant by the clinical pharmacist. Of these 415 (67%) were drug-drug interactions, 207 (33%) were dosage alerts and 1 (0%) was an allergy (figure 2). Pharmacy technicians assessed 76% of the alerts as non-relevant alerts according to local procedures. Most common reported reasons for acceptance of the alert by the technicians were the following: dosage is conform guidelines and pharmacotherapeutic handbooks (n=166), drug-drug interactions for continuation of pre-admission therapy (n=73) and alert is not relevant for the individual patient considering the dose of the drug or co-medication (n=35). An information leaflet, containing recommendations to prevent patient harm, was sent to the ward for 15% of the alerts and 9% of the alerts were submitted to a hospital pharmacist. The hospital pharmacist proposed an intervention, such as change in drug therapy or additional monitoring, to the responsible physician for 10 of those 56 alerts of which 7 were considered relevant by the physician.

**Table 4:** Characteristics of drug-related problems detected by a clinical pharmacist only (n=407), versus drug-related problems detected by a clinical pharmacist and CPOE/CDSS (n=35)

| | Problems detected by | | |
|---|---|---|---|
| **Characteristic of drug-related problem** | **Clinical pharmacist only n=407 n (%)** | **Clinical pharmacist and CPOE n=35 n (%)** | **Statistics** |
| Class of drug-related problem | | | **p = 0.02**[a] |
| Indication | 145 (36) | 8 (23) | |
| Effectiveness | 53 (13) | 8 (23) | |
| Safety | 39 (10) | 8 (23) | |
| Pharmaceutical care issues | 170 (42) | 11 (31) | |
| Severity of drug-related problem | | | p = 0.24[a] |
| Non-relevant problem | 149 (37) | 8 (23) | |
| Relevant problem, no harm | 105 (26) | 10 (29) | |
| Relevant problem, harm | 153 (38) | 17 (49) | |
| Relevant drug-related problem according to physician | 261 (64) | 25 (71) | p = 0.39[a] |
| Acceptance of proposed interventions | 223 (55) | 24 (69) | p = 0.12[a] |
| Therapeutic area of drug-related problem | | | Not applicable[b] |
| Gastro-intestinal tract (A) | 53 (13) | 2 (6) | |
| Blood system (B) | 55 (14) | 2 (6) | |
| Cardiovascular tract (C) | 52 (13) | 11 (31) | |
| Dermatologicals (D) | 2 (1) | 0 (0) | |
| Genitourinary systems and sex hormones (G) | 6 (2) | 0 (0) | |
| Hormonal systemic therapy (H) | 8 (2) | 2 (6) | |
| Anti-infectives (J) | 51 (13) | 1 (3) | |
| Cancer therapy (L) | 2 (1) | 0 (0) | |
| Musculo-skeletal system (M) | 28 (7) | 2 (6) | |
| Nervous system (N) | 99 (24) | 11 (31) | |
| Anti-parasitic products, insecticides and repellents (P) | 3 (1) | 0 (0) | |
| Respiratory tract (R) | 30 (7) | 4 (11) | |
| Sensory organs (S) | 13 (3) | 0 (0) | |
| Various (V) | 5 (1) | 0 (0) | |
| Female gender | 172 (43) | 20 (57) | p = 0.09[a] |
| Age (years; median, IQR) | 72 (17) | 71 (22) | p = 0.73[c] |
| Number of drugs during admission (median, IQR) | 16 (10) | 15 (5) | p = 0.29[c] |
| Number of drugs at time of medication review (median, IQR) | 12 (6) | 12 (6) | p = 0.55[c] |
| Length of stay (days; median, IQR) | 10 (14) | 9 (12) | p = 0.52[c] |
| Medical ward | | | |
| Surgery (versus neurology) | 314 (77) | 30 (86) | p = 0.24[a] |

IQR = interquartile range; RR = relative risk; 95%CI = 95% confidence interval
Figures in bold are statistically significant
[a] Chi-square test
[b] Chi-square test could not be applied, due to low observed count and expected count <5 in many cells
[c] Mann–Whitney U test

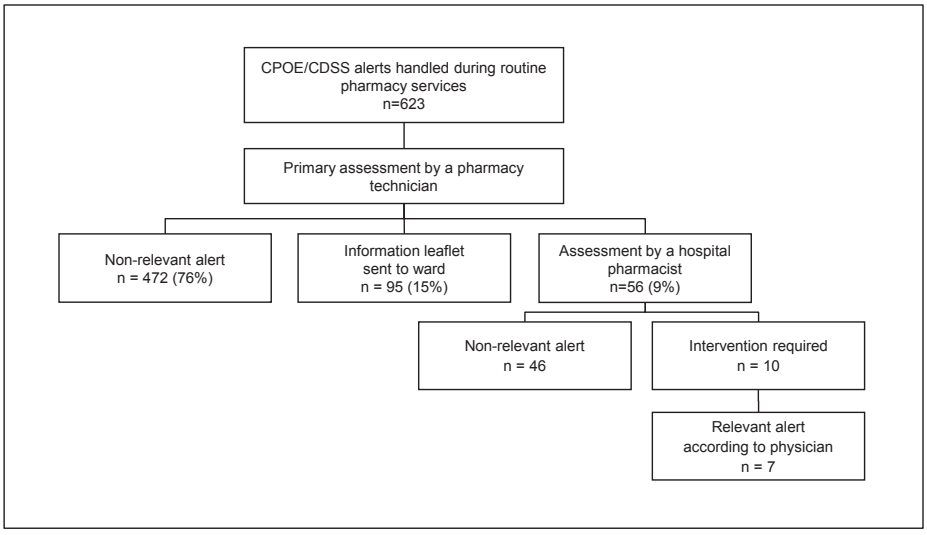


**Figure 2:** Handling of additional CPOE/CDSS alerts during routine pharmacy services

## DISCUSSION

To our knowledge, this is the first study looking at the effect of a clinical pharmacist on the identification of drug-related problems in addition to routine use of CPOE/CDSS. It shows that a clinical pharmacist can identify drug-related problems that are not detected by basic CPOE/CDSS. This is consistent with previous findings that drug-related problems still occur after implementation of CPOE/CDSS[20, 23, 42, 43] and that a clinical pharmacist can improve medication safety in different health care settings.[27, 44]

Only 8% of the drug-related problems identified by the clinical pharmacist generated a CPOE/CDSS alert. Problems that did generate an alert and those that did not differed only with respect to the class of the drug-related problem. The clinical pharmacist identified many problems regarding indication (mainly unnecessary drug therapy) and pharmaceutical care (especially discrepancies with pre-admission pharmacotherapy and requirement for additional monitoring). By contrast, the CDSS, that covers basic principles of support only, generated relatively more alerts for problems concerning safety (e.g. overdosage), effectiveness (e.g. underdosage) and drug-drug interactions. This is in line with our expectations since the system is not programmed to identify problems regarding indication and pharmaceutical care issues other than drug-drug interactions and allergies.

Currently, more sophisticated CDSSs that use clinical rules to detect pharmacotherapeutic errors are being developed and implemented in the Netherlands.[17, 45, 46] Examples of such clinical rules are the following: prescription of a drug which requires dosage adjustment for a patient with renal failure, no laxative prescribed in conjunction with

opioid use and no ulcer protection prescribed to a patient >70 years who uses an NSAID. Van Doormaal et al. reported that 39% of the dosing and therapeutic errors detected by a retrospective medication review by a pharmacist were detected by a small set of clinical rules. When these clinical rules were combined with CPOE/CDSS this proportion increased to 66%.[19] However, we believe that a clinical pharmacist may still contribute to the reduction of drug-related problems even when more clinical rules are used. For example by reviewing a patients complete pharmacotherapy to identify unnecessary drugs or certain adverse drug reactions, which will probably not be completely possible with CPOE/CDSS or clinical rules in the near future.

For patients in our study, CPOE/CDSS generated many additional alerts that the clinical pharmacist did not identify or did not consider relevant. Most of these alerts were handled by pharmacy technicians during routine central pharmacy care and did not require an intervention. Only about 10% of CPOE/CDSS alerts needed assessment by a pharmacist and even for these alerts an intervention was not always required, suggesting that CPOE/CDSS has a low positive predictive value to identify drug-related problems that require an intervention. In contrast, the majority of the problems identified by the clinical pharmacist, who focused on problems that required an intervention, were considered relevant by the attending physician. As a result, most of the proposed interventions to ameliorate the problems were accepted, suggesting that a clinical pharmacist identifies and averts more clinically relevant drug-related problems than basic CPOE/CDSS.

Our study has four limitations. The first is that only patients with one or more identified drug-related problems according to the clinical pharmacists were included in the analysis, which means that CPOE/CDSS alerts for patients without any drug-related problems according to the clinical pharmacist were not included. Consequently, we could not calculate the specificity and sensitivity to identify drug-related problems by medication review and by CPOE/CDSS alerts or the positive and negative predictive values.

Second, neither the actual reduction of patient harm by the clinical pharmacist nor the cost-effectiveness of this intervention was assessed.

Third, the clinical pharmacist was aware of the limitations of basic CDSS and could have focused more on problems that are not detected by CPOE/CDSS. But as the aim of our study was to identify which drug-related problems can be identified by a clinical pharmacist in a setting with routine use of CPOE/CDSS, we feel this fact represents the way a clinical pharmacist operates in real life and thus generates results that are representative for daily routine.

Fourth, because organizational characteristics have been shown to be a determinant for drug-related problems, these results cannot be extrapolated to other medical specialties or hospitals with a differently organized pharmaceutical care or to hospitals using other CPOE/CDSSs. Main strength of this study is that the discussion with the attending

physician yielded information about the clinical relevance of the identified problems and the acceptance of the proposed interventions for individual patients.

Future studies should focus on optimizing the sensitivity and specificity of CPOE/CDSSs incorporating clinical rules to detect clinically relevant drug-related problems by combining data from different electronic health records. Furthermore, the contribution of clinical pharmacists in addition to these advanced systems should be assessed, as well as their cost-effectiveness and potential to reduce actual harm.

To identify and avert drug-related problems routine hospital pharmacy service should be much more patient-focused than drug-focused. It should consist of medication reconciliation at admission, central handling of CPOE/CDSS alerts, a defined set of clinical rules, and medication review by a clinical pharmacist and the attending physician. Besides, advanced health information technologies that help physicians, clinical pharmacists and other health care professionals to identify patients at risk of drug-related problems should be designed and implemented. These technologies should fit into clinical workflow and minimize alerts for problems that are not clinically relevant and do not require an intervention.

To conclude, a clinical pharmacist can identify many additional drug-related problems in a setting with routine use of CPOE/CDSS. On the other hand CPOE/CDSS generates many alerts that are not considered relevant. These findings should be used to develop more advanced CDSSs to identify drug-related problems. Given the type of drug- related problems identified by clinical pharmacists when compared to CDSS, clinical pharmacists may still provide additional value even in settings using more advanced CDSSs.

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# 6

# Medication review using a Systematic Tool to Reduce Inappropriate Prescribing (STRIP) in adults with an intellectual disability: a pilot study

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## ABSTRACT

### Background

A Systematic Tool to Reduce Inappropriate Prescribing (STRIP), which includes the Screening Tool to Alert doctors to Right Treatment (START) and the Screening Tool of Older Peoples' Prescriptions (STOPP), has recently been developed in the Netherlands for older patients with polypharmacy in the general population. Active involvement of the patient is part of this systematic multidisciplinary medication review. Although annual review of pharmacotherapy is recommended for people with an intellectual disability (ID), a specific tool for this population is not yet available. Besides, active involvement can be compromised by ID. The objective of this observational pilot study was to evaluate the process of medication review using STRIP in adults with an ID living in a centralized or dependent setting and the identification of drug-related problems using this tool.

### Method

The study was performed in three residential care organizations for ID. In each organization nine clients with polypharmacy were selected by an investigator (a physician in training to become a specialized physician for individuals with an ID) for a review using STRIP. Clients as well as their legal representatives (usually a family member) and professional caregivers were invited to participate. Reviews were performed by an investigator together with a pharmacist. First, to evaluate the process time-investments of the investigator and the pharmacist were described. Besides, the proportion of reviews in which a client and/or his legal representative participated was calculated as well as the proportion of professional caregivers that participated. Second, to evaluate the identification of drug-related problems using STRIP, the proportion of clients with at least one drug-related problem was calculated.

### Results

Mean time investment was 130 minutes for the investigator and 90 minutes for the pharmacist. The client and/or a legal representatives were present during 25 of 27 reviews (93%). All 27 professional caregivers (100%) were involved. For every client included at least one drug-related problem was identified. In total 127 drug-related problems were detected, mainly potentially inappropriate or unnecessary drugs. After six months, 15.7% of the interventions were actually implemented.

### Conclusions

Medication review using STRIP seems feasible in adults with an ID and identifies drug-related problems. However, in this pilot study the implementation rate of suggested interventions was low. To improve the implementation rate, the treating physician should be involved in the review process. Besides, specific adaptations to STRIP to address drug-related problems specific for this population are required.

## INTRODUCTION

Polypharmacy, defined as the concomitant use of five or more drugs, can be indicated in case of multimorbidity, but it is also an important risk factor for undesired health outcomes in the general population, including adverse drug events[1], hospitalizations[2] and mortality.[3] In our earlier work, published in this journal, we showed that polypharmacy is an important risk factor for clinically relevant prescription errors in older individuals with an intellectual disability (ID).[4]

Individuals with an ID are prone to polypharmacy due to the high prevalence of chronic comorbid conditions. These include somatic diseases, such as gastrointestinal disorders[5-7] and epilepsy[7], the presence of cardiovascular risk factors[8, 9], and mental conditions, such as behavioral problems, sleep disturbances[10], anxiety[11] and depression.[12] In previous studies the prevalence of polypharmacy among individuals with an ID varied between 11% and 60%, depending on the study population, definitions and study methods.[13] Although different prescribing guidelines for the ID population acknowledge the risk of polypharmacy, clear recommendations to prevent or reduce polypharmacy are lacking or focus on psychotropic medication only.[13]

Besides polypharmacy, both impaired cognition and living in a residential care setting have been identified as independent risk factors for medication related hospital admissions in the general population.[2] As these risk factors are pertinent in the residential ID population, the Dutch Health Care Inspectorate demands an annual reassessment of pharmacotherapy by the physician, pharmacist, professional caregiver and the individual or his legal representative.[14]

In the Netherlands a multidisciplinary guideline has been developed for reviewing pharmacotherapy in older persons with polypharmacy[15], called the Systematic Tool to Reduce Inappropriate Prescribing (STRIP). This method comprises five steps: a pharmacotherapeutic history, including experiences and expectations of the patient (1), an analysis of potential drug-related problems, in which the Screening Tool to Alert doctors to Right Treatment (START) and the Screening Tool of Older Peoples' Prescriptions (STOPP) with adaptations to Dutch practice are being used (2)[16, 17], proposing a pharmaceutical care plan by the physician and the pharmacist (3), concordance between physician and patient on the care plan (4), and follow-up (5). However, a validated instrument to perform a review in individuals with an ID is not available. A recent Dutch study performed by Scheifes et al. evaluated a comparable structured medication review (not including START and STOPP criteria) performed by pharmacists and psychiatrists in individuals with an ID and severe behavioral problems.[18] This study showed that structured medication review is a valuable tool to identify drug-related problems and optimize pharmacotherapy. However, the authors noted that the participation of patients in the pharmaceutical anamnesis was problematic, that patients' understanding of the questions about their pharmacotherapy

might be insufficient and that patients are prone to give socially desirable answers. It is known that in the ID-population atypical symptoms of diseases, which can be masked by the disability, and persons' inability to communicate about disease complicate diagnosing, prescribing and evaluating pharmacotherapy.[19, 20] In addition, their knowledge on potential adverse drug reactions and alternatives to medication seems limited [21] and their capacity to consent with treatment is often impaired.[22, 23] As a result, active involvement of adults with ID in the evaluation of their pharmacotherapy (step 1) and concordance (step 4) in a medication review using STRIP could be complicated as well, but ways to involve and empower individuals with ID despite these problems should be explored. Therefore, the objectives of this study were to evaluate the process of medication review using STRIP in adults with an ID living in a residential care setting and the identification of drug-related problems.

## METHODS

### Design

A pilot study was performed to explore the process of medication review using STRIP in adults with an ID.

### Setting and study population

This study was performed in three Dutch residential care organizations for adults with an ID (DeSeizoenen (Oploo), Het Raamwerk (Noordwijkerhout), Pluryn (Nijmegen)). These organizations provide residential care, including reimbursed chronic specialized healthcare, provided by a team of certified physicians for individuals with an intellectual disability (ID-physicians), behavioral therapists, physiotherapists and other disciplines. Daily support and care, including administering medication, is given by a team of professionally trained caregivers. Until recently, professional training of these caregivers primarily focused at behavioral aspects and less on health and nursing. The treating ID-physician is responsible for the medical care, including pharmacotherapy. In the Netherlands, the legal representative of a client, who is usually a family member, needs to give consent to any changes in (medical) treatment. Preferably, the client agrees with the treatment as well.

Since this study did not affect patient integrity, a waiver from the Medical Ethics Committee was obtained.

### Data collection

The three different pharmacists connected to the care organizations selected all clients with polypharmacy, defined as the concomitant use of five or more drugs, from their organization. In each care organization one of three investigators, who were physicians following

the 3-year specialist training to become an ID-physician, selected nine adults to obtain a sample with large diversity in age, level of disability and comorbid conditions. Selected clients, their legal representatives and professional caregivers received written information about the pilot study and were invited for an interview about their pharmacotherapy.

The medication reviews were performed in June 2013 (organization 1), July and September 2013 (organization 2) and October 2013 (organization 3). Gender, age and level of ID (mild, intelligence quotient (IQ) ≥55 to <70; moderate, IQ ≥35 to <55 and severe, IQ<35) of included adults were recorded by the investigators. Number and type of drugs (according to Anatomical Therapeutic Chemical (ATC) classification system) at time of the review were extracted from the records of the dispensing pharmacy.

The investigators did not have any responsibilities in patient care during the study.

## The Systematic Tool to Reduce Inappropriate Prescribing (STRIP)

The medication review process is described in detail in table 1. Reviews were performed by the investigator together with a pharmacist, following the steps described in the detailed description of the tool. The review included the Screening Tool to Alert doctors to Right Treatment (START) (appendix A) to identify potentially appropriate indicated drugs that should be started and the Screening Tool of Older Peoples' Prescriptions (STOPP) (appendix B) to identify potentially inappropriate or unnecessary drugs that should be withheld. Apart from the explicit START and STOPP criteria, additional drug-related problems were identified by the pharmacist or the investigator based on their professional judgement and

**Table 1:** Reviewing pharmacotherapy according to the Systematic Tool to Reduce Inappropriate Prescribing

| | Description | Performed by |
|---|---|---|
| Preliminary phase | Collecting relevant data on pharmacotherapy, allergies, medical history, current diagnoses, laboratory results | Investigator |
| Step 1 | During an interview with the client and/or his legal representative or his professional caregiver, the investigators collected information on the actual pharmacotherapy and the clients experiences and expectations. | Investigator |
| Step 2 | Potential drug-related problems were identified using data obtained during the previous steps. | Pharmacist |
| Step 3 | Composing a pharmaceutical care plan in which treatment goals, relevant drug-related problems and interventions were defined. | Investigator together with pharmacist |
| Step 4 | Concordance with the client and/or his legal representative on the care plan. | Investigator |
| Step 5 | Follow-up: Discussing the findings in a meeting with the treating ID-physician. Implementation of the suggested interventions to optimize pharmacotherapy was assessed directly, three and six months after the review process. | Investigator |

current guidelines on appropriate prescribing in ID[24] or the general population.[25, 26]These additional drug-related problems were classified as potentially appropriate indicated drugs, potentially inappropriate or unnecessary drugs, drug use problems, monitoring issues and discrepancies (for example between the patient information, medical record and/or the pharmacy record).

Suggestions to improve pharmacotherapy were discussed with the treating ID-physician. Implementation of suggested interventions to change pharmacotherapy was assessed immediately after the review, after three months and after six months by reviewing clients' pharmacy records.

## Financial consequences

Time invested by the investigator and the pharmacists was recorded during the review process. Costs related to their efforts were calculated using an hourly rate of €45 for the pharmacist, based on the maximum salary costs for employed pharmacists[27] and €54 for the resident ID-physician (based on the maximum salary costs of an ID-physician).[28]

Medication-related costs/savings of interventions to resolve drug-related problems were calculated using the consumer reimbursement price published on the website of the National Health Care Institute.[29] These prices are based on the pharmacist purchase price minus 6.82% clawback (a rate the pharmacist has to pay to the healthcare insurance company to compensate for purchase discounts with a maximum of €6.80 per prescription) plus 6% value-added tax. The dispensing fee for the pharmacist is excluded in this price. The difference in costs for the prescribed drug before the intervention and the prescribed drug after the intervention was calculated for all interventions and the financial consequences were recalculated using 67% of these total cost differences, assuming an implementation rate of 67%. This assumption was based on previous studies in which the acceptance rates of pharmacists' interventions in hospitalized patients varies between 56 and 98%.[30-35]

Total financial consequences were calculated by summing the salary costs and the difference in drug costs. Costs for additional monitoring were excluded from this analysis.

Additionally, cost differences were calculated for every intervention partly or completely implemented that resulted in a change of pharmacotherapy six months after the review. Again, total financial consequences were calculated by summing the salary costs and the difference in drug costs.

## Outcomes

First, to evaluate the process of medication review using STRIP in the ID-population time-investments of the investigator and the pharmacist were described. Besides, the proportion of reviews in which a client and/or his legal representative participated was calculated as well as the proportion of professional caregivers that participated (based

on the requirement of the Dutch Health Care Inspectorate that these persons should be involved in medication review in individuals with an ID[14]).

Second, to evaluate the identification of drug-related problems using STRIP, the proportion of clients with at least one drug-related problem was calculated. Additional outcomes in this evaluation were the number and types of drug-related problems identified, the implementation rate of suggested changes in pharmacotherapy directly, three months and six months after the review, the net savings on direct pharmaceutical costs assuming an implementation rate of 67% and the net savings of interventions that were partially or completely implemented six months after the review.

### Statistical analysis

Data were analyzed using IBM SPSS Statistics version 21.0. Descriptive statistics were used to determine the participation of adults with ID, their legal representatives and professional caregivers as well as the number and types of potential drug-related problems. Financial consequences were calculated using Microsoft Excel version 2010.

## RESULTS

### Evaluation of the process of medication review using STRIP

#### *Study population*

During this pilot-study 27 reviews were performed. Characteristics of the included clients are presented in table 2. For these clients a comparable structured medication review using STRIP had not been performed before. The median number of drugs used per client was 10 (range 5-29), including as needed prescriptions. Twenty-one clients (77.8%) had at least one as needed prescription (median 1; range 0-7), mostly drugs acting on the central nervous system (13 clients) and drugs for the alimentary tract (8 clients).

**Table 2:** Characteristics of included clients (n=27)

| **Patient characteristics** | **n (%)** |
|---|---|
| Female gender | 13 (48.1) |
| Age, years (median, range) | 45 (18-80) |
| Level of intellectual disability | |
| Mild | 13 (48.1) |
| Moderate | 9 (33.3) |
| Severe | 5 (18.5) |
| Number of drugs (median, range) | 10 (5-29) |
| Number of drug-related problems (median, range) | 4 (1-12) |

Details on the drug use per pharmacotherapeutic group are presented in table 3. Almost all patients used drugs for the alimentary tract (26 clients) and drugs acting on the central nervous system (24 clients).

**Table 3:** Use of drugs according to pharmacotherapeutic group

| | Patients (n=27) using ≥ 1 drugs from class |
|---|---|
| **Pharmacotherapeutic group**[a] | **n (%)** |
| Alimentary tract and metabolism (A) | 26 (96.3) |
| Blood and blood forming organs (B) | 8 (29.6) |
| Cardiovascular system (C) | 14 (51.9) |
| Dermatologicals (D) | 11 (40.7) |
| Systemic hormonal preparations (H) | 6 (22.2) |
| Anti-infectives for systemic use (J) | 3 (11.1) |
| Musculo-skeletal system (M) | 3 (11.1) |
| Nervous system (N) | 24 (88.9) |
| Respiratory system (R) | 5 (18.5) |
| Sensory Organs (S) | 5 (18.5) |

[a] According to Anatomical Therapeutic Chemical (ATC) classification system

### *Time investment*

The mean time investment of investigators per client was 30 minutes for the preliminary phase, 30 minutes for step 1, 40 minutes for step 3, 20 minutes for step 4 and 10 minutes for step 5. Mean total time investment for the investigators was 130 minutes. Mean time investments for the pharmacists was 60 minutes in step 2 and 30 minutes in step 3 and thus 90 minutes in total.

### *Involvement of clients, legal representatives and professional caregivers*

In total 24 out of 27 (89%) clients were present during the medication review. Of the three clients that did not participate two had a mild disability and one had a severe disability. For two of these clients participation in the review was considered too stressful given their disabilities. The other client developed psychotic symptoms during the interview and left the interview early. The client and/or a legal representatives were present during 25 of 27 reviews (93%). All 27 professional caregivers (100%) were involved.

## Identification of drug-related problems

### *Identified drug-related problems and implementation of interventions*

For each client included at least one drug-related problem was identified and in total 127 drug-related problems were identified. (table 4). During the review process 4 potentially

**Table 4:** Identified potential drug-related problems (n=127)

| Potential drug-related problem | n | (%) | Example |
|---|---|---|---|
| Potentially appropriate indicated drug (START) | 4 | (3.1) | Oral anticoagulant indicated with chronic atrial fibrillation |
| Potentially appropriate indicated drug | 2 | (1.6) | Laxative indicated for constipation; insulin indicated for diabetes mellitus type II poorly controlled with oral antidiabetic drugs |
| Potentially inappropriate or unnecessary drug (STOPP) | 18 | (14.1) | Duplicate therapy with 4 antiepileptic drugs or 2 antipsychotic drugs |
| Potentially inappropriate or unnecessary drug | 81 | (63.8) | Underdose of vitamin D; ineffective drug (NSAID) prescribed for neuropathic pain; unnecessary drugs given the present condition, e.g. proton pump inhibitor, antihistamine, dermal preparations |
| Drug use problem | 6 | (4.7) | Infrequent use of carbomer liquid eye gel to relieve dryness; infrequent use of cleansing enema for constipation |
| Monitoring | 15 | (11.8) | Control of serum levels of antiepileptics or potassium level required; measuring of blood pressure is recommended |
| Discrepancy | 1 | (0.8) | Use of hydrocortisone ointment by client is unknown to physician and pharmacist |
| Total | 127 | (100.0) | |

NSAID, non-steroidal anti-inflammatory drug

appropriate indicated drugs were identified by START in 4 clients (15% of our population) and 18 potentially inappropriate or unnecessary drugs were identified by STOPP in 13 clients (48% of our population). Apart from the START and STOPP criteria, the pharmacist and the investigator identified 2 potentially appropriate indicated drugs, 81 potentially inappropriate or unnecessary drugs, 6 drug-use problems, 15 monitoring issues and 1 discrepancy. Examples of the identified problems are presented in table 4. In total 32 problems (25.4%) were related to drugs acting on the central nervous system, including potentially unnecessary drug therapy without a clear indication (n=13), potentially inappropriate drug therapy due to the presence of an adverse drug reaction (n=6) or supratherapeutic dosage (n=4) and requirement of monitoring (n=4).

### *Implementation rate of suggested interventions*

The implementation rate of the suggested interventions for the 127 problems is presented in table 5. Directly after the review 5 (3.9%) of the 127 interventions had been partially implemented. The implementation rate increased to 13.4% three months after the review. After six months, 20 out of 127 proposed interventions (15.7%) had been partially or completely implemented.

**Table 5:** Implementation rate of interventions (n=127) to resolve potential drug-related problems

| Implementation | After review n (%)[&] | After 3 months n (%)[&] | After 6 months n (%)[&] |
|---|---|---|---|
| Complete | 3 (2.4) | 13 (10.2) | 14 (11.0) |
| Partly | 2 (1.6) | 4 (3.1) | 6 (4.7) |
| Not implemented | 90 (70.9) | 76 (59.8) | 73 (57.5) |
| Unknown* | 28 (22.0) | 28 (22.0) | 28 (22.0) |
| Loss to follow-up[#] | 4 (3.1) | 6 (4.7) | 6 (4.7) |

[&] Percentages of total number of interventions (n=127)
* For example: monitoring of blood pressure control or serum drug levels could not be evaluated in this study
[#] Two clients died shortly after the review and were lost to follow-up

### *Financial consequences*

Mean time investment per review was 130 minutes for the investigator and 90 minutes for the pharmacist, resulting in a total of €184.50 salary costs per review and € 4981.50 for 27 reviews.

From all 127 interventions medication-related costs/savings could be calculated for 88 interventions. Apart from additional monitoring (n=15), medication-related costs/savings could not be calculated for 24 interventions because the specific drug, dose or frequency used or advised was unknown or the drug was not available on the website of the National Health Care Institute. The 88 interventions included in this analysis would result in a reduction of € 38,234.97 in medication related costs yearly. In case of an implementation rate of 67%; the net savings on pharmaceutical costs of the review process would be

€ 38,234.97*0.67- € 4981.50 = € 20,635.93. However, it should be mentioned that this benefit was strongly influenced by one drug-related problem, namely duplicate therapy of tadalafil and bosentan for pulmonary hypertension in one client. Discontinuation of one of these two drugs would result in a benefit of €30,773.87. Exclusion of this benefit would mean that the review process would yield ((€38,234.97-€30,773.87)*0.67) - €4981.50=€17.44.

For three of the 20 interventions that were at least partly implemented after six months the medication-related costs/savings could not be calculated (no specific drug was advised, the drug was not available on the website of the National Health Care Institute or the drug-related problem concerned a drug allergy that was not recorded in the pharmacy chart). The remaining 17 changes in pharmacotherapy that were actually implemented after six months resulted in a reduction of €2024.91 in yearly drug costs, meaning that for this scenario the costs for the review process are €4981.50 - €2024.91= €2956.59.

## DISCUSSION

In this pilot study we showed that the Systematic Tool to Reduce Inappropriate Prescribing can be used for adults with an ID to identify drug-related problems. Medication review using this tool requires substantial time investments from physicians and pharmacists. It should be mentioned that neither these physicians nor the pharmacists used STRIP for this specific population before this pilot study. When STRIP would be implemented as routine practice for the annual assessment of pharmacotherapy, both the physician and the pharmacist would gain experience in using this tool, resulting in a decrease in time investment. Moreover, a first medication review for a patient takes significantly more time, since the patient's medical and pharmaceutical history need to be collected. When implementing structured medication review in practice, one should consider delegating some tasks in the preliminary phase to other professionals, such as professional caregivers. In the only published study on medication review in adults with an intellectual disability and severe behavioral problems, time investments were substantially lower, namely one hour for the pharmacist and physician together.[18] However, in this study the pharmaceutical history with the client was performed by the nurse. Besides, differences between settings, such as available data in the medical record, and training of the professionals could possibly explain these differences.

During almost all reviews the client and/or a legal representative were present and a high number of individuals with an ID in residential care were able to be involved in a systematic medication review. This may be explained by the fact that most participants had a mild to moderate degree of ID. Although the actual contribution of the clients to the identification of drug-related problems has not been systematically recorded in this study, the investigators mentioned the added value of involving the client, since clients spontaneously reported adverse events. Besides, investigators noted that the clients appreciated being involved in the process, which possibly could improve their adherence to pharmacotherapy. In comparison, during home medication review by community pharmacists in older patients with polypharmacy using medication and clinical records as well as an interview with the patient, about one quarter of all drug-related problems, mostly adverse drug reactions, were identified during the interview,[36] suggesting important contribution of the patients themselves.

All professional caregivers were involved in the process. They experienced the medication review process as useful. For example, the evaluation of actual use of as needed prescriptions showed that some of these drugs were not used at the right moment or were not used at all.

A total of 127 drug-related problems, mainly potentially unnecessary or inappropriate drugs, were detected and for all 27 included adults at least one drug-related problem was identified. In the previously mentioned study on structured medication review in

clients with severe behavioral problems, drug-related problems were identified in 80% of included clients, mostly potentially unnecessary drugs (i.e. drugs with no or an unclear indication).[18] In previous studies performed in the general population in primary care settings or nursing homes using START and STOPP criteria, potentially appropriate indicated drugs were identified in 42 to 50% of the older patients and potentially inappropriate or unnecessary drugs in 27 to 60% of the older patients.[37-39] In our pilot study, potentially appropriate indicated drugs according to START criteria were identified less often than in these studies. The proportion of clients with potentially inappropriate or unnecessary drugs according to STOPP criteria found in our study seems comparable to that in the general population, but a large number of the potentially inappropriate or unnecessary drugs were identified by other means than the STOPP criteria. This suggests that the actual prevalence of unnecessary or inappropriate drugs could even be higher than in the general population, emphasizing the need for adaptation of the STOPP criteria for the ID population. However, given the small sample size of our pilot study, no definite conclusions can be drawn from our study.

STRIP, including the START and STOPP criteria used in this systematic medication review, was designed for individuals aged 65 years and older in the general population. We used it for adults, aged 18 years and older, with an ID. Because age-related frailty starts at a younger age, around 50 years, in the ID-population[40, 41] one could argue that START and STOPP criteria could be applicable to adults with ID from around 50 years and older. Although the median age in our pilot study was slightly below 50 years, relatively few problems were identified by the START or STOPP criteria. Future research in individuals with an ID should explore which items of the START and STOPP criteria are relevant for adults with an ID and which adaptations, in accordance with specific guidelines, such as the international guide to prescribing psychotropic medication for the management of problem behaviors,[42] are necessary. For example, duplicate therapy of drugs acting on the central nervous system (e.g. two or more antiepileptics for epilepsy or two or more antipsychotics for behavioral problems) could be added to the STOPP-criteria and supplementation of vitamin D could be added to the START-criteria. Besides, one should focus on evaluating the effect and adverse events of chronic drug treatment and the actual use of "as needed" prescriptions. An adapted tool should especially emphasize evaluation of antipsychotics, which are used by up to 45% of individuals with an ID[42] and require extensive monitoring on potential adverse drug reactions, including involuntary movements and for the newer antipsychotics weight gain and metabolic syndrome.[43] Moreover, there is a special need to evaluate the effectiveness and the actual reason for prescription of antipsychotics according to the international guidelines,[42] since almost 80% of the antipsychotics are used longer than 10 years, often without a clear indication.[44]

In this study only 15.7% of the suggested interventions were at least partly implemented six months after the review (criterion 4), whereas Scheifes et al. reported an implementa-

tion rate of 56.9%.[18] Presence of an indication for a potentially unnecessary drug, change of physician, attention for the treatment relationship and early discharge were reported as reasons for not implementing interventions. However, the reason for not implementing was unknown in 18 of 44 not-implemented interventions. Moreover, acceptance rates of interventions based on START-criteria and STOPP-criteria above 90% have been reported in older hospitalized patients.[45] The fact that the reviews in our study were performed by physicians, not being the treating physician, could have influenced the low implementation rate in our setting. Therefore, we recommend involvement of the treating physician in any medication review. Unfortunately, we did not assess physicians' reasons for not implementing the suggested interventions. Since the interventions were proposed by a physician in training to become an ID-physician together with a pharmacist we believe the recommendations (e.g. discontinuation of potentially inappropriate or unnecessary drugs) were feasible in general. However, the treating physician could have argued that a recommendation was not applicable to the specific patient; comparable to the physicians in the previously mentioned study, where the physicians did find an indication for potentially unnecessary drugs. Besides, attention for the treatment relationship or opinions of professional caregivers (especially on discontinuation of drugs for behavioral problems) could have played a role. In addition, preferences of clients or their legal representatives could have hindered implementation, since legal representative need to give consent to changes in pharmacotherapy in the Netherlands. Moreover, most clients visit different specialists because of their multimorbidity, and the treating physicians could have thought they were not able to implement changes to pharmacotherapy initiated by another specialist. However, in other settings, other barriers for implementing changes could exist, depending on the legal responsibilities, especially when clients have the right to make their own decisions when they are capable, as in England and Wales.[23] It should be mentioned that physicians in general could be accountable for not following evidence-based guidelines, unless valid argumentation for disregarding evidence-based recommendations is well documented in the medical record.

Assuming an implementation rate of 67%, the review results in net savings on pharmaceutical costs. However, looking at the changes in pharmacotherapy that were actually implemented, the medication review using STRIP did not result in net savings on pharmaceutical costs, as the salary costs were higher than the benefits in medication costs. This can be explained by the relatively few interventions that were actually implemented by the treating physician and the substantial time investments discussed earlier. Additionally, we used the maximum salary costs for both the physician and the pharmacist as a worst case scenario, whereas actual salary costs may be lower. Since our study was a pilot study a sensitivity analysis was not performed for the financial consequences. Considering the presented example of duplicate therapy of tadalafil and bosentan, single drug-related problems could have major impact on the financial consequences. Therefore, future larger

studies should focus on the cost-effectiveness of medication review, including sensitivity analyses. However, probably comparable outliers (problems related to expensive drugs) will be identified in other studies.

This study has five main limitations. First, given the small sample size of this pilot study, no definite conclusions can be drawn on the prevalence of drug-related problems and the cost-effectiveness of STRIP. In addition, the clients were not randomly selected, which could have resulted in sampling bias. Therefore, the sample may not be representative for the population of adults with an ID in residential care settings.

Second, we did not assess inter-rater reliability between the three physicians or the three pharmacists. Given the absence of specific recommendations and guidelines on polypharmacy for the ID-population this inter-rater reliability may be a problem, which should be addressed in future studies.

Third, reviews were performed by investigators who were not the treating physicians. This might have influenced the implementation rate as well as the time investment and financial consequences. Fourth, we did not take into account actual harm caused by the drug-related problems and the reduction in patient harm by the review process. Finally, experiences of the clients, legal representatives, professional caregivers, physicians and pharmacists were not systematically studied.

Notwithstanding these limitations, to our knowledge this is one of the first studies on a systematic multidisciplinary medication review in adults with an ID with polypharmacy. Besides, the study was performed in three care organizations, improving the generalizability of the results.

To conclude, this pilot study shows that medication review using the Systematic Tool to Reduce Inappropriate Prescribing can be used in adults with an ID to identify drug-related problems. In this pilot study the implementation rate of interventions was low. To improve the implementation rate, the treating physician should be involved in the review process. Future studies should focus on specific adaptations to STRIP (including START and STOPP criteria) for this population, the cost-effectiveness, reduction of actual patient harm and experiences of the clients, their legal representatives and involved professionals using this tool.

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**Appendix A** START criteria

| |
|---|
| Cardiovascular system |
| ACE inhibitor (or Angiotensin II receptor blocker) with chronic heart failure |
| ACE inhibitor (or Angiotensin II receptor blocker) with diabetes mellitus with proteinuria and life expectancy >10 years |
| ACE inhibitor (or Angiotensin II receptor blocker) following acute myocardial infarction |
| Statin therapy with history of coronary, cerebral, or peripheral vascular disease, following acute myocardial infarction or with diabetes mellitus and LDL > 2,5 mmol/l |
| Antihypertensive therapy with systolic blood pressure > 160 mm Hg |
| Diuretics with chronic heart failure |
| β-blocker with stable angina pectoris, following acute myocardial infarction or stable chronic heart failure (low dose) |
| Salicylate with chronic atrial fibrillation and contra-indication for oral anticoagulants, with chronic stable angina pectoris or following acute myocardial infarction |
| Salicylate and/or clopidogrel with history of coronary, cerebral or peripheral vascular disease and sinus rhythm |
| Oral anticoagulants with chronic atrial fibrillation |
| Respiratory system |
| Inhalation of short-acting β-2 agonist or anticholinergic agent for mild to moderate asthma or COPD |
| Inhalation of corticosteroids for moderate to severe asthma or COPD (GOLD III-V and predicted FEV1<50% with ≥2 exacerbations per year) |
| Oxygen therapy with chronic respiratory failure |
| Central nervous system |
| Levodopa with Parkinson's disease with functional limitations or handicaps |
| Antidepressants with depression (according to DSM IV-criteria) |
| Gastro-intestinal system |
| Proton pump inhibitor with severe gastro-oesophagal reflux disease or peptic stricture requiring dilatation |
| Proton pump inhibitor with NSAID plus history of peptic ulcer, age ≥ 70 years or age 60-70 years and concomitant use of oral anticoagulants, oral glucocorticosteroid, SSRI or salicylate |
| Proton pump inhibitor with low dose salicylate and age ≥ 60 years with history of peptic ulcer, ≥ 70 years and concomitant use of oral anticoagulants, oral glucocorticosteroid or SSRI or age ≥ 80 years |
| Fiber supplement with chronic symptomatic diverticulosis with obstipation |
| Musculoskeletal system |
| DMARD with active moderate to severe rheumatoid arthritis (>4 weeks) |
| Bisphosphonates in patients taking glucocorticosteroids >3 months |
| Calcium and vitamin D supplement in patients with osteoporosis or patients with risk at osteoporosis |
| Endocrine system |
| Metformin with type 2 diabetes mellitus |
| ACE inhibitor or Angiotensin II receptor blocker with diabetes mellitus and nefropathy |
| Antiplatelet therapy with diabetes mellitus and proven cardiovascular disease |
| Statin therapy with diabetes mellitus and cardiovascular risk factors |
| Other |
| Laxatives with opiod use |

Adapted to the Dutch practice by Vermeulen Windsant-van den Tweel et al. [17] from Gallagher et al [16]
ACE, angiotensin converting enzyme; LDL, low density lipoproteins; COPD, Chronic Obstructive Pulmonary Disease; FEV1, forced expiratory volume; DSM IV, Diagnostic and Statistical Manual of Mental Disorders; NSAID, non-steroidal anti-inflammatory drugs; SSRI, Selective serotonin re-uptake inhibitors; DMARD, disease modifying antirheumatic drug

**Appendix B** STOPP criteria

| |
|---|
| Cardiovascular system |
| Digoxin >0,125 mg per day with impaired renal function |
| Loop diuretic for ankle edema only, without clinical sings of heart failure or for hypertension |
| Thiazide diuretic with a history of gout |
| Non-selective β-blocker (propranolol, carvedilol, oxprenolol, pindolol, labetalol, sotalol) with COPD |
| β-blocker in combination with verapamil |
| Diltiazem or verapamil with chronic heart failure NYHA class III or IV |
| Calcium channel blockers with chronic obstipation |
| Salicylates >160 mg per day or without coronary, cerebral or peripheral arterial symptoms or for dizziness not related to cerebrovascular disease |
| Dipyridamol as monotherapy for secondary cardiovascular prevention |
| Oral anticoagulants for longer than 6 months duration for first uncomplicated deep vein thrombosis or for longer than 12 months duration for first uncomplicated pulmonary embolus |
| Platelet inhibitors or oral anticoagulants with bleeding disorders |
| Central nervous system |
| Tricyclic antidepressant with dementia, glaucoma, cardiac conduction diseases, obstipation, prostatism, history of urinary retention or with an opiate or calcium channel blocker |
| Long-acting benzodiazepines for longer than 1 month duration |
| Antipsychotics with parkinsonism or for longer than 1 month duration |
| Phenothiazines with epilepsia |
| Parasympathicolytic anti-Parkinson drugs for extrapyridamal effects of antipsychotics |
| SSRIs with non-iatrogenic hyponatremia in the previous two months |
| First generation antihistamines for longer than one week duration |
| Gastro-intestinal system |
| Loperamide or codein for diarrhea e.c.i. or for severe infectious gastro-enteritis |
| Metoclopramide with parkinsonism |
| Proton pump inhibitor for peptic ulcer disease at full therapeutic dose >8 weeks |
| Butylscopolamine with chronic obstipation |
| Respiratory system |
| Theophylline as monotherapy for COPD |
| Systemic instead of inhaled glucocorticosteroids for maintenance therapy of moderate-severe COPD |
| Ipratropium or tiotropium with glaucoma |
| Musculoskeletal system |
| NSAID with moderate to severe hypertension, heart failure, chronic renal failure, for mild joint pain in ostheoarthritis for longer than 3 months duration, for maintenance therapy of gout for longer than 3 months duration without contraindication or proven inefficacy for allopurinol |
| Glucocorticoids as monotherapy for rheumatoid arthritis or osteoarthritis for longer than 3 months duration |
| Colchicin for maintenance therapy of gout for longer than 3 months duration without contraindication or proven inefficacy of allopurinol |
| Urogenital system |
| Bladder antimuscarinic drugs with dementia, chronic glaucoma, chronic obstipation, chronic miction problems |
| Selective α1-blocker for men with daily incontinence or urinary catheter in situ for longer than 2 months duration |
| Endocrine system |
| Glibenclamide for type 2 diabetes mellitus |
| Neuroleptics, classic antihistamines, long-acting opiates and vasodilator drugs for patients with a history of orthostatic hypotension |
| Non-selective β-blocker (propranolol, carvedilol, oxprenolol, pindolol, labetalol, sotalol) with diabetes mellitus and frequent hypoglycemia (>1 episode per month) |
| Estrogen replacement therapy with history of breast cancer or history of thromboembolism or as monotherapy, without prostagens, in women with intact uterus. |
| Mobility |
| Benzodiazepines, neuroleptics, first generation antihistamines and long acting opiates for those prone to falls |
| Vasodilator drugs in those with postural hypotension |
| Pain |
| Opiates as long term first-line treatment for mild to moderate pain or with dementia |
| Other |
| Duplicate therapy |

Adapted to the Dutch practice by Vermeulen Windsant-van den Tweel et al. [17] from Gallagher et al [16]

# 7

# Physicians' acceptance of pharmacists' interventions from central pharmacy services in daily hospital practice

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## ABSTRACT

### Background

Detailed knowledge on the acceptance rate of pharmacists' interventions in daily clinical practice and determinants for acceptance in particular is important to optimize both pharmacotherapy and central pharmacy services.

### Objective

To determine the physicians' acceptance rate of pharmacists' interventions from central pharmacy services in routine daily hospital practice and to identify determinants for acceptance.

### Methods

A retrospective case-control study was performed in adult patients admitted to a university hospital in the Netherlands. Pharmacists' interventions, based on alerts for drug-drug interactions and drug dosing in patients with renal failure, recorded in the electronic medical record from January 2012 until June 2013 were extracted. The primary outcome was the proportion of accepted interventions, which was assessed by reviewing the computerized physician order entry system and electronic medical records. A mixed-effects logistic model was used to identify determinants for physicians' acceptance as secondary outcome.

### Results

A total of 841 interventions relating to 623 patients were included. Drug-drug interactions (46.4%), supratherapeutic dosages (21.8%) and requirement of additional drug therapy (8.7%) were the most common underlying drug-related problems.

Physicians accepted 599 interventions, resulting in an acceptance rate of 71.2%. The mixed-effects logistic model showed that acceptance was significantly associated with the number of drugs (16 to ≤20 drugs $OR_{adj}$ 1.88; 95% CI 1.05-3.35, >20 drugs $OR_{adj}$ 2.90; 95% CI 1.41-5.96, both compared to ≤10 drugs) and severity of the drug-related problem (drug-related problems without potential harm $OR_{adj}$ 6.36; 95% CI 1.89-21.38; drug related with potential harm OR 6.78; 95% CI 2.09-21.99, both compared to clinically irrelevant problems), and inversely associated with continuation of pre-admission treatment ($OR_{adj}$ 0.55; 95% CI 0.35-0.87).

### Conclusion

The majority of pharmacists' interventions from a central pharmacy setting are accepted by physicians and the probability for acceptance increases for patients with an increasing number of medication orders and for clinically relevant problems. Interventions regarding continued pre-admission treatment are less likely to be accepted.

## INTRODUCTION

Reviewing medication orders, using clinical decision support systems (CDSS) and clinical rules, in order to prevent drug-related problems is part of the daily routine of clinical pharmacists. In general, recommendations to optimize pharmacotherapy for clinically relevant drug-related problems are proposed to the attending physician. The physicians' acceptance rate of these pharmacists' interventions has been shown to vary between 52% and 98% in previous studies.[1-14] This variation can probably be explained by differences in setting, such as the prescribing process (computerized or handwritten), the identification of potential drug-related problems (using CDSS or medication review) and the way of communicating the intervention (by telephone, during ward rounds and/or electronically recorded). Most of these studies dealt with recommendations proposed during ward rounds by clinical pharmacists who were, at least partly, integrated in the medical team on the ward. However, in daily routine practice a substantial number of interventions are proposed from the central pharmacy by telephone, at least in the Netherlands and surrounding countries in continental Europe.

In a recent French multicentre study on pharmacists' interventions a subset of interventions was proposed by pharmacists from the central pharmacy by telephone. The acceptance rate in this subset of interventions was 62%.[3] However, interventions were extracted from a national database designed for documentation and classification of interventions during daily medication review. Since the number of interventions varied strongly between pharmacists, wards and hospitals, it is likely that not all interventions were documented.

Consequently, the acceptance rate of pharmacists' interventions from the central pharmacy and communicated by telephone is not exactly known. Besides, little is known about the characteristics that determine the acceptance of pharmacist's interventions proposed during daily routine from the central pharmacy.

Further insight into the determinants for acceptance could facilitate optimizing the central pharmacy services aimed at reducing drug-related problems and improving pharmacotherapy. Therefore, the objectives of this study were to determine the acceptance rate of pharmacists' interventions proposed by telephone from the central pharmacy, and to identify determinants for acceptance.

## METHODS

### Design and setting

This study was designed as a retrospective case-control study, performed in a university hospital in the Netherlands. In this hospital, medication is prescribed using a computerized physician order entry system (Medicator®, CSC-Isoft, Leiden, The Netherlands) combined

with a basic clinical decision support system, based on the Dutch national drug database G-standard® (Z-Index, The Hague, The Netherlands). This system generates intrusive alerts (pop-ups) during prescribing for overdosing, duplicate therapy, allergies and drug-drug interactions during prescribing. Nevertheless, a substantial amount of these alerts are handled incorrectly or overridden unconsciously by physicians.[15] Reviewing alerts for drug-drug interactions is part of the daily routine of pharmacists in our central pharmacy. Besides, a clinical rule is used to assess drug dosing in patients with renal failure. All medication orders of patients identified by this clinical rule are reviewed by a pharmacist. Subsequently, for all relevant drug-related problems a recommendation to resolve the specific problem is proposed to the physician by telephone. All these interventions are recorded in a special tab of the patient's electronic medical record.

## Data collection

All interventions recorded in the electronic medical record during weekdays from January 2012 until July 2013 resulting from drug-drug interactions and the clinical rule renal failure were included in this study. In exceptional cases, when the treating physician could not be contacted, interventions were communicated by e-mail. These interventions were excluded from this study. Interventions for patients admitted to intensive care units, are usually not proposed from the central pharmacy, since a clinical pharmacist is present on these wards.

Data on the intervention (date, weekday, number of days since drug-related problem arose), the underlying drug-related problem (group of drug involved according to the Anatomical Therapeutic Chemical (ATC) classification system and whether the drug was continued from pre-admission treatment or initiated during admission), characteristics of the patient involved (age, gender, renal failure (glomerular filtration rate < 50 ml/min), number of drugs at time of intervention, length of stay at time of intervention), characteristics of the pharmacist (gender and status (resident versus certified clinical pharmacist) and medical specialty of the prescriber were recorded. All patient data were processed anonymously in a protected database. Since this study did not affect patient integrity, a waiver of the Medical Ethical Committee was obtained for this study.

## Drug-related problems and interventions

Drug-related problems were classified according to the classification of Strand et al.[16], that was adapted by Leendertse et al.[17] This classification differentiates drug-related problems regarding the indication (additional drug therapy required or unnecessary drug therapy), effectiveness (ineffective drug therapy or subtherapeutic dosage), safety (adverse drug event or supratherapeutic dosage), drug use problems, and pharmaceutical care issues (monitoring, drug-drug interactions, contra-indicated drug, lifestyle, duplicate therapy). We added discrepancies with pre-admission treatment and administrative prescribing er-

rors (i.e. missing information on drug, dosage or administration route or duplicate orders) to this classification based on our clinical experience.

The severity of drug-related problems was assessed using the NCC-MERP index, classifying severity from clinically irrelevant problems (A), that have the capacity to cause problems, to problems that may contribute to or result in death (I).[18] We grouped these categories into three classes, namely clinically irrelevant drug-related problems, drug-related problems without potential harm, and drug-related problems with potential harm, varying from mild temporary discomfort to death. Because of the intervention, actual harm was prevented and therefore potential harm was assessed, by estimating the consequences of the drug-related problem, in case the pharmacist would not have intervened. The assessment was performed by both a hospital pharmacist/clinical pharmacologist and a physician/clinical pharmacologist. After their independent assessment they discussed all discrepancies to reach consensus.

Interventions were classified according to the classification used by Bedouch et al.[19] as drug choice (addition of a drug, discontinuation of a drug or drug switch), dose adjustment (increasing the dose, decreasing the dose), monitoring (which we subdivided into therapeutic drug monitoring, monitoring of biochemical parameters, recording an electrocardiogram and other types of monitoring) and optimization of administration (which we defined as optimization of administration times). Based on our experience we added an additional class with other expected interventions, including consulting another specialist, reconciliation of pre-admission treatment or administrative interventions.

## Outcomes

Primary outcome was the proportion of accepted interventions. Acceptance of interventions regarding drug choice, dose adjustments or optimization of administration was assessed by reviewing the computerized physician order entry system. Acceptance was defined as implementation of the suggested change in pharmacotherapy within 24 hours. For interventions regarding monitoring clinical chemical parameters, serum drug levels or electrocardiogram the medical record was reviewed; interventions were considered as accepted when the suggested test was performed within 7 days. Monitoring of other adverse drug events, for example oedema, symptoms of heart failure or myalgia, could not be assessed in this study.

Characteristics of the intervention (type of intervention, day of the week and number of days since problem arose), the underlying drug-related problem (pharmacotherapeutic group of drug involved according to anatomical therapeutic chemical classification system (ATC), severity and continuation of pre-admission treatment), characteristics of the patient involved (gender, age, presence of renal failure (glomerular filtration rate < 50 ml/min), number of drugs at time of intervention and length of stay at time of intervention), characteristics of the pharmacist (gender and status (resident versus certified hospital

pharmacist)) and the medical specialty of the prescriber (medical, surgical, intensive care or cardiology) were included as potential determinants for acceptance.

### Statistical analysis

Considering an expected acceptance rate of 60% and 15 potential predictors the minimum required sample size was 375 interventions.

Descriptive analyses were performed using IBM SPPS Statistics version 21. A logistic mixed-effects logistic model was performed with R statistical software version 3.2.2 (www.r-project.org) to investigate associations between potential determinants and acceptance, while accounting for multiple interventions within the same patients. The advantage of using mixed-effect models is that they can deal with unbalanced datasets, namely when the number of available observations per patient, that could be measured at different time points, varies. To ease the interpretation of the results, the continuous variables age, number of drugs and length of stay were categorized into four categories, based on the quartiles of their frequencies. Adjusted odds ratios, corrected for the other covariates, with 95% confidence intervals were calculated. A p-value <0.05 was considered statistically significant.

## RESULTS

A total of 841 interventions, involving 623 patients were included. Characteristics of these interventions and patients are presented in table 1. Drug-drug interactions (46.4%), supratherapeutic dosages (21.8%) and requirement of additional drug therapy (8.7%)

**Table 1:** Characteristics of included patients and interventions included

| | n (%) |
|---|---|
| Patients | **623 (100.0)** |
| Gender | |
| Female | 263 (42.2) |
| Male | 360 (57.8) |
| Age in years, median [range] | 64.0 [18-91] |
| DRPs per patient, median [range] | 1.0 [1-6] |
| Proposed interventions | **841 (100.0)** |
| Medical specialty prescriber, n (%) | |
| Medical wards | 449 (53.4) |
| Surgical wards | 231 (27.5) |
| Intensive Care Units | 1* (0.1) |
| Cardiology Units | 160 (19.0) |

* At the time of proposing the intervention the patient was transferred to an intensive care unit

were the most common underlying drug-related problems (table 2). Interventions were proposed most frequently for problems related to anti-infective agents (33.9%), drugs acting on blood and blood forming organs (13.4%) and drugs for alimentary tract and metabolism (12.2%) (table 3).

**Table 2:** Drug-related problems underlying pharmacists' interventions (n=841)

| Class | Subclass of drug-related problem | n (%) |
|---|---|---|
| Indication | Additional drug therapy required | 73 (8.7) |
| | Unnecessary drug therapy | 3 (0.4) |
| Effectiveness | Ineffective drug therapy | 8 (1.0) |
| | Dosage too low | 45 (5.4) |
| Safety | Dosage too high | 183 (21.8) |
| | Adverse drug event | 8 (1.0) |
| Drug use | Drug use problem | 13 (1.5) |
| Pharmaceutical Care | Drug-drug interaction | 390 (46.4) |
| | Contra-indication | 64 (7.6) |
| | Duplicate therapy | 25 (3.0) |
| | Monitoring | 11 (1.3) |
| | Discrepancy with pre-admission pharmacotherapy | 8 (1.0) |
| | Administrative prescribing errors | 10 (1.2) |
| **Total** | | **841 (100.0)** |

**Table 3:** Pharmacotherapeutic drug group underlying pharmacists' interventions (n=841)

| Pharmacotherapeutic group* | n (%) |
|---|---|
| Alimentary tract and metabolism (A) | 103 (12.2) |
| Blood and blood forming organs (B) | 113 (13.4) |
| Cardiovascular system (C) | 69 (8.2) |
| Anti-infective agentsfor systemic use (J) | 285 (33.9) |
| Antineoplastic and immunomodulating agents (L) | 33 (3.9) |
| Musculo-skeletal system (M) | 94 (11.2) |
| Nervous system (N) | 86 (10.2) |
| Other[a] | 58 (6.9) |
| **Total** | **841 (100.0)** |

* According to Anatomical Therapeutic Chemical (ATC) Classification System

[a] Includes dermatologicals (D), genito-urinary system and sex hormones (G), systemic hormonal preparations (H), antiparasitic products (P) and respiratory system (R).

After consensus between two clinical pharmacologists 569 (67.7%) drug-related problems were assessed as clinically relevant problems having potential to cause patient harm, whereas 253 (30.1%) of the problems were unlikely to cause harm; 19 (2.3%) problems were considered as clinically irrelevant.

**Table 4:** Mixed-effects model showing the association between potential determinants and acceptance of pharmacists' interventions (n=769)[§]

| Potential determinant | $OR_{adj}$ | 95% CI | p-value |
|---|---|---|---|
| ***Characteristics of intervention*** | | | |
| Sequential count of interventions per patient | 1.00 | 0.77-1.31 | 0.976 |
| Type of intervention | | | |
| Addition of a drug | ref. | | |
| Discontinuation of a drug | 1.17 | 0.45-3.03 | 0.745 |
| Drug switch | 0.57 | 0.25-1.27 | 0.168 |
| Increasing the dose | 0.75 | 0.26-2.16 | 0.588 |
| Decreasing the dose | 0.81 | 0.33-2.01 | 0.653 |
| Therapeutic Drug Monitoring | 0.47 | 0.16-1.41 | 0.179 |
| Monitoring of biochemical parameters | 0.53 | 0.19-1.45 | 0.219 |
| Recording an electrocardiogram | 0.33 | 0.10-1.08 | 0.067 |
| Optimization of administration times | 1.06 | 0.33-3.57 | 0.930 |
| Weekday of intervention | | | |
| Monday | ref. | | |
| Tuesday | 2.34 | 0.88-6.20 | 0.087 |
| Wednesday | 1.24 | 0.69-2.22 | 0.473 |
| Thursday | 0.83 | 0.45-1.50 | 0.532 |
| Friday | 0.94 | 0.51-1.74 | 0.852 |
| Number of days since problem arose | 0.93 | 0.76-1.14 | 0.477 |
| ***Characteristics of underlying drug-related problem**** | | | |
| Pharmacotherapeutic group of drug involved | | | |
| Alimentary tract and metabolism (A) | ref | | |
| Blood and blood system (B) | 0.72 | 0.33-1.60 | 0.423 |
| Cardiovascular system (C) | 1.05 | 0.44-2.49 | 0.912 |
| Anti-infectives for systemic use (J) | 0.84 | 0.41-1.69 | 0.628 |
| Antineoplastics and immunomodulating agents (L) | 0.43 | 0.15-1.26 | 0.123 |
| Musculo-skeletal system (M) | 0.58 | 0.26-1.30 | 0.185 |
| Nervous system (N) | 0.65 | 0.27-1.52 | 0.320 |
| Other[#] | 0.57 | 0.23-1.41 | 0.220 |
| Severity | | | |
| Clinically irrelevant drug-related problem | ref. | | |
| Relevant problem without potential harm | **6.36** | **1.89-21.38** | **0.002** |
| Relevant problem with potential harm | **6.78** | **2.09-21.99** | **0.001** |
| Continuation of pre-admission treatment (hospital-initiated treatment is reference) | **0.55** | **0.35-0.87** | **0.010** |
| ***Patient characteristics*** | | | |
| Female gender | 0.86 | 0.58-1.27 | 0.443 |
| Age (years) | | | |
| ≤ 50 | 0.66 | 0.38-1.13 | 0.126 |
| 51 to ≤ 65 | 0.91 | 0.50-1.65 | 0.759 |
| 66 to ≤ 75 | 0.92 | 0.47-1.79 | 0.796 |
| > 75 | | | |
| Presence of renal failure | 1.10 | 0.70-1.73 | 0.676 |
| Number of drugs | | | |
| ≤ 10 | ref. | | |
| 11 to ≤ 15 | 1.63 | 0.94-2.81 | 0.082 |
| 16 to ≤ 20 | **1.88** | **1.05-3.35** | **0.033** |
| > 20 | **2.90** | **1.41-5.96** | **0.004** |
| Length of stay (days) | | | |
| ≤ 1 | ref. | | |
| 2 to ≤ 3 | 0.65 | 0.38-1.12 | 0.123 |
| 4 to ≤ 8 | 0.98 | 0.54-1.76 | 0.936 |
| > 8 | 0.80 | 0.44-1.46 | 0.461 |
| ***Pharmacists' characteristics*** | | | |
| Female gender | 1.53 | 0.89-2.60 | 0.122 |
| Residents (certified hospital pharmacists are reference) | 0.95 | 0.62-1.45 | 0.804 |
| ***Medical specialty of prescriber*** | | | |
| Medical | ref. | | |
| Surgical | 1.14 | 0.71-1.84 | 0.589 |
| Cardiology | 1.09 | 0.65-1.82 | 0.754 |

Figures in bold are statistically significant

OR, odds ratio; CI, confidence interval; ref, reference; DRP, drug-related problem

§ Excluding interventions for which acceptance could not be assessed (n=51). Subsequently, interventions with missing data (renal function (n=11) and continuation of pre-admission treatment (n=6)) and interventions for intensive care units (n=1) and intervention types "consulting another specialist" (n=2) or "administrative interventions" (n=1) were excluded from the mixed-effects model as well.

* According to Anatomical Therapeutic Chemical (ATC) Classification System

[#] Includes dermal preparations (D), genito-urinary system and sex hormones (G), systemic hormonal preparations (H), antiparasitic products (P) and respiratory system (R).

599 of the 841 included interventions were accepted, resulting in a physicians' acceptance rate of 71.2 %, whereas 191 (22.7%) interventions were not accepted and acceptance could not be assessed for 51 (6.1%) interventions.

The mixed-effects logistic model used to explore associations between potential determinants and acceptance is presented in table 4. Physicians' acceptance was significantly associated with the number of drugs (16 to ≤20 drugs $OR_{adj}$ 1.88; 95% CI 1.05-3.35, >20 drugs $OR_{adj}$ 2.90; 95% CI 1.41-5.96) and severity of the drug-related problem (drug-related problems without potential harm $OR_{adj}$ 6.36; 95% CI 1.89-21.38; drug related with potential harm $OR_{adj}$ 6.78; 95% CI 2.09-21.99), and inversely associated with continuation of pre-admission treatment ($OR_{adj}$ 0.55; 95% CI 0.35-0.87).

## DISCUSSION

In this study physicians' acceptance rate of pharmacists' interventions was 71.2% and the number of medication orders at time of the intervention, the continuation of pre-admission treatment and the severity of the underlying drug-related problem were statistically significant associated with acceptance.

Our acceptance rate is somewhat higher than the acceptance rate of 62% in a subset of interventions proposed by pharmacists from a central pharmacy reported in a large multicenter study.[3] Others reported even lower acceptance rates of around 50%.[6, 12, 13] The accurate assessment of the clinical relevance of potential drug-related problems by our pharmacists, illustrated by the small number of clinically irrelevant alerts, could be an explanation for the higher acceptance rate found in our study. In addition, other differences in settings, such as the communication methods, the system for detecting the drug-related problems and physicians' attitude towards pharmacists, could have contributed to the higher acceptance rate .

It should be noted that our acceptance rate is comparable with some reported acceptance rates of around 60% to 80% in settings with pharmacists integrated in the medical team on the ward.[3, 13, 20] Therefore, central checking of CDSS alerts and clinical rules could be considered for settings with pharmacists on the ward, so the pharmacist on the ward can focus on other drug-related problems, such as adverse drug reactions.

In our study, the number of medication orders of a patient at time of the intervention was significantly associated with acceptance. Possibly, physicians have less overview of a patients' complete pharmacotherapy when the number of medication orders increases and they are more inclined to accept an intervention. This suggests an added value of pharmacists for patients with polypharmacy, which is imaginable since polypharmacy is a well-known risk factor for drug-related problems.[21]

Furthermore, the probability for acceptance decreases if the underlying drug had been initiated before admission, indicating that physicians may be reluctant to change medication initiated by another physician before admission, which could be explained by the physicians' confidence in the expertise of their colleagues.

Our finding that interventions for drug-related problems assessed as clinically relevant by two clinical pharmacologists are more likely to be accepted, suggests that physicians do give careful consideration to the clinical relevance of a problem, based on their knowledge and experience, weighing the risks and benefits for the individual patient. Apparently, their judgement is in accordance with the assessment of the clinical pharmacologists when they decide not to accept the intervention. However, this finding was based on only 19 interventions and should be interpreted with caution.

We did not find an association between any other characteristics of the intervention, the underlying problem, the patient or the prescriber. In addition, we found no difference in acceptance rates between pharmacy residents and certified hospital pharmacists. Probably, physicians are not aware of the status of the pharmacists, indicating that our residents are well trained to review pharmacotherapy, assess the clinical relevance of drug-related problems and propose interventions to physicians. However, the finding that some of the drug-related problems were assessed as clinically irrelevant, not requiring an intervention, according to clinical pharmacologists, shows variability between different professionals during the medication review process, despite of training and use of guidelines. Still, the small number of irrelevant interventions shows that our pharmacists are trained to assess the relevance of the majority of potential drug-related problems.

In contrast to our results, Bedouch et al showed a significant association between several therapeutic drug classes and acceptance.[3] Besides, some previous studies have shown differences in acceptance between surgical and medical wards.[3, 8, 22] We were not able to reproduce these results, which can probably be explained by differences in setting and the smaller sample size of our study.

In our setting, interventions were discussed between the pharmacist and the physician by telephone. Subsequently, pharmacists recorded their interventions in the patient's electronic medical record. Looking at the patients included in our study, the pharmacy tab in their electronic medical records was viewed 5568 times in total; 96.9% of these were views by pharmacists and only 3.1% by physicians. This indicates that physicians decisions to accept interventions are based on the discussion, since they hardly viewed the recorded recommendations. Previously, it has been shown that interventions that are only recorded electronically are much less likely to be accepted than verbally communicated interventions.[20] This is confirmed by a recent Spanish study, in which the authors found a lower acceptance rate of 53% for interventions that were communicated electronically.[6] These findings support the current process of proposing interventions for the studied drug-related problems by telephone from the central pharmacy.

Our study has several main limitations. First, this study is retrospective and hence reasons for non-acceptance were unknown. Physicians may have valid arguments to decline a recommendation, but we were not able to retrieve their argumentation.

Second, the proportion of the proposed interventions of the total CDSS alerts is unknown. This proportion could vary between different pharmacists and settings and can influence the acceptance rate. For example, when a pharmacist decides to propose only the most urgent interventions the acceptance rate could increase.

Third, this study is performed in only one hospital and the results are difficult to extrapolate to other hospitals, especially when the pharmacists are more integrated on the ward.

Fourth, we were not able to include any characteristics of the prescriber, except for specialty, whereas physicians' status (resident versus specialist) has been associated with acceptance previously.[20]

Despite these limitations, this is one of the first studies on the acceptance of pharmacists' interventions and determinants for acceptance in a setting that is representative for settings with central pharmacy services.

Future research should focus on reasons for non-acceptance, for which prospective follow-up of interventions and exploring physicians' reasons for non-acceptance is recommended, with the ultimate goal to adapt interventions for specific problems according to the specialty of the prescriber. Furthermore, clinical consequences of non-acceptance in terms of patient harm, length of stay and pharmaceutical costs need to be studied.

To improve clinical pharmacy services, we recommend pharmacists and physicians in primary and secondary care to discuss their responsibilities on chronic pharmacotherapy during admission of a patient, based on our finding that physicians tend to decline interventions regarding medication initiated before admission. It is conceivable that non-urgent recommendations are discussed by the pharmacist with the patients' general practitioner. In more urgent cases cases pharmacists should be aware of physicians' declined propensity to accept recommendations and should use more convincing arguments during the discussion. Stronger arguments should also be used for patients with less than 10 drugs to increase the acceptance of interventions for these patients. On the other hand, pharmacists could more pro-actively review the complete pharmacotherapy of patients using more than 15 or 20 drugs, to detect more drug-related problems and optimize therapy together with the physician.

In conclusion, the majority of pharmacists' interventions from a central pharmacy setting are accepted by physicians and the probability for acceptance increases for patients with an increasing number of medication orders and for relevant drug-related problems. Interventions regarding continued pre-admission treatment are less likely to be accepted. To optimize central pharmacy services further insight into physicians' reasons for non-acceptance is necessary.

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# 8

# Physicians' barriers and facilitators for accepting pharmacists' interventions

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## ABSTRACT

### Background

During daily routine, clinical pharmacists propose changes in pharmacotherapy to reduce potential drug-related problems. To optimize physicians' acceptance of these interventions understanding physicians' barriers and facilitators for acceptance is essential.

### Objective

To explore physicians' barriers and facilitators for acceptance of pharmacists' interventions.

### Methods

An explorative study was conducted in a university hospital, using a short questionnaire. Randomly selected physicians, 12 residents and 12 specialists form both medical and surgical wards, were asked to estimate their acceptance rate of pharmacists' interventions. Subsequently, they were questioned on their perceived barriers and facilitators for acceptance and their opinion on pharmacists' interventions.

The mean self-reported acceptance rate was calculated and Mann–Whitney U tests were used to compare the rates between medical physicians and surgeons and between residents and specialists. Reported barriers and facilitators were classified into the categories knowledge, attitude and behavior.

### Results

Forty-eight interviews were conducted and forty-seven interviews were analysed. The mean reported acceptance rate was 88.3% (95% confidence interval (CI) 83.9-92.7). The reported acceptance rate differed significantly between medical physicians and surgical physicians (81.3% versus 96.4%, $p<0.001$), but not between residents and specialists (89.6% versus 86.6%, $p=0.718$).

In total 47 barriers and 40 facilitators for acceptance were mentioned, mostly related to physicians' attitude. Inapplicability of a recommendation to the individual patient was the most frequently reported barrier (n=20) and confidence in the pharmacist was the most frequently reported facilitator (n=16).

### Conclusion

In general, physicians report to accept the majority of pharmacists' interventions. Most barriers and facilitators for acceptance were related to physicians' attitude. To optimize the acceptance rate to eventually reduce drug-related problems, pharmacists need to take these barriers and facilitators into account.

## INTRODUCTION

Proposing changes in pharmacotherapy to physicians to reduce potential drug-related problems and optimize therapy is an important part of the daily routine of clinical pharmacists. Previous studies have shown that between 52% and 98% of pharmacists' interventions for hospitalized patients are actually accepted by the physician.[1-13] The nature of the underlying drug-related problem, the pharmacotherapeutic group of the drug involved, the type of intervention, characteristics of the physician (status and medical specialty), characteristics of the pharmacist (the integration of the pharmacist on the ward and status) and the way of communicating have been associated with the acceptance rate in previous studies.[3, 11, 14, 15] However, physicians' reasons to decline or accept a specific intervention for an individual patient have not been systematically addressed in these studies.

Since pharmacists' interventions are mainly based on evidence-based guidelines, a comparison with the uptake of evidence in clinical care in general could be made. It is recognized that implementing evidence-based guidelines and changing established patterns of care requires multi-strategy approaches, acknowledging potential barriers and facilitators on different levels of healthcare.

One of these levels is that of the individual physicians. Cabana et al. proposed a model, describing in detail the barriers of individual physicians that result in their non-adherence to evidence-based guidelines.[16] These barriers can reflect physicians' knowledge (lack of awareness or lack of familiarity) or attitude (lack of agreement, lack of self-efficacy, lack of outcome expectancy or so-called " inertia of previous practice" (i.e. habit and routines)). Besides, external barriers, such as patient factors and environmental factors, can influence physicians' actual behavior. Cabana's model has been used successfully in different studies to explore physicians' barriers to adhere to guidelines.[17, 18] Physicians' facilitators, their decision to change, are often the opposites of potential barriers.

In addition, May et al. proposed a general theory of implementation, describing the incorporation of the intervention into clinical practice and the social system, which requires workable interventions and individual and collective commitment of healthcare professionals and patients as well as their sustainable investments in operationalizing the required actions.[19]

Summarizing, detailed knowledge on physicians' barriers and facilitators for change is thought to be essential for designing an effective intervention to improve implementation of evidence-based recommendations.[20] Similarly, further understanding of physicians' barriers and facilitators for accepting pharmacists' interventions is important to improve clinical pharmacy services. Therefore, the objectives of this study were to explore physicians' barriers and facilitators for acceptance of pharmacists' interventions in hospital care.

## METHODS

### Design and setting

This study was designed as an explorative questionnaire study and was performed in a university hospital in the Netherlands. In this hospital, medication is prescribed using a computerized physician order entry system (Medicator®, CSC-Isoft, Leiden, The Netherlands) combined with a basic clinical decision support system, based on the Dutch national drug database G-standard® (Z-Index, The Hague, The Netherlands). During prescribing this system generates intrusive alerts (pop-ups) for overdosing, allergies, contra-indications, duplicate therapy and drug-drug interactions, which are nevertheless often ignored by physicians.[21] Reviewing ignored alerts for drug-drug interactions is part of the daily routine of clinical pharmacist in the central pharmacy. In addition, a clinical rule is used to assess drug dosing in patients with renal failure. For relevant drug-related problems detected by these alerts and the clinical rule that require a change in pharmacotherapy or additional monitoring, the clinical pharmacist intervenes and gives recommendations to the responsible physician, usually a resident, by telephone. All these interventions are recorded in a special form of the electronic medical patient record.

### Data collection and physicians

Data were collected by telephone interviews with individual physicians using an open-ended questionnaire. Interviews were performed between July 2013 and June 2014 by pharmacists or pharmacy interns with randomly selected residents and attending specialists from medical and surgical wards. The questions were open-ended and dealt with the following topics: acceptance, barriers and facilitators and physicians' opinion on pharmacists' interventions (table 1). Answers to the questions were noted during the interview.

Derived from a previous study, showing that data saturation occurs within 12 in-depth interviews for qualitative research [22], we included 12 medical residents, 12 medical specialists, 12 surgical residents and 12 surgeons. Participating physicians were asked for the

**Table 1:** Questionnaire on physicians' experiences and opinions of pharmacists' interventions

| Topic | | Question |
|---|---|---|
| Acceptance, barriers and facilitators | 1 | Could you estimate which percentage of pharmacists' interventions you accept? |
| | 2 | What are your reasons for not accepting an intervention? |
| | 3 | What are your reasons to accept an intervention? |
| Content | 4 | What's your general opinion on the pharmacists' interventions? |
| | 5 | Do you think the interventions are relevant? |
| | 6 | Are the interventions clear? |
| | 7 | Are the interventions feasible? |

following characteristics: gender, medical specialty (medical versus surgical) and status (resident versus specialist).

## Classification of barriers and facilitators

Reported barriers for acceptance (question 2) were classified by two reviewers until consensus was reached according to the model proposed by Cabana et al., which we adapted slightly to fit with pharmacists' interventions.[16] Similarly, physicians' facilitators for acceptance (question 3) were defined by rewording the barriers. The adapted model is presented in table 2.

**Table 2:** Barriers and facilitators for acceptance of pharmacists' interventions (based on the model of Cabana et al.[16])

| Level | Sublevel | Barrier | Facilitator |
|---|---|---|---|
| Knowledge | Familiarity | - Lack of familiarity | - Familiarity or aware of own lack of familiarity |
| | Awareness | - Lack of awareness | - Awareness or aware of own lack of knowledge |
| Attitude | Agreement with specific intervention | - Lack of agreement with interpretation of evidence<br>- Inapplicable to patient<br>- Lack of confidence in pharmacist | - Agreement with interpretation of evidence<br>- Applicable to patient<br>- Confidence in pharmacist |
| | Agreement with interventions in general | - Too rigid to apply<br>- Not practical<br>- Challenge to autonomy | - Not too rigid to apply<br>- Practical<br>- No challenge to autonomy |
| | Outcome expectancy | - Physician believes that recommendation will not lead to desired outcome | - Physician believes that intervention will lead to desired outcome |
| | Self-efficacy | - Physician believes he/she cannot perform the recommendation | - Physicians believes that he/she can perform intervention |
| | Motivation-Inertia of previous practice | - Habit/Routines | - Not hampered by habit/routines |
| Behavior | Patient factors | - Inability to reconcile patient preferences with intervention | - Patient preferences can be reconciled with intervention |
| | Intervention factors | - Intervention characteristics<br>- Presence of contradictory recommendations | - Intervention characteristics<br>- No contradictory recommendations |
| | Environmental factors | - Lack of time<br>- Lack of resources<br>- Organizational constraints<br>- Lack of reimbursement<br>- Perceived increase in malpractice liability | - Sufficient time<br>- Sufficient resources<br>- No organizational constraints<br>- No financial constraints<br>- No perceived increase in liability |

Answers to questions on general opinion about the interventions (question 4), the relevance (question 5), the clearness (questions 6) and the feasibility (questions 7) of interventions were classified as positive, neutral or negative by the same two reviewers until consensus was reached. The proportion of physicians with a positive opinion was calculated.

## Data analysis

The mean self-reported acceptance rate with 95% confidence intervals (question 1) was calculated, using SPSS version 21. Mann–Whitney U tests were used to compare these reported rates between medical physicians and surgeons and between residents and specialists. A p-value of 0.025 (after using Bonferroni correction for multiple testing) was considered as statistically significant.

## Results

Forty-eight physicians were interviewed as planned, namely 12 medical residents, 12 medical specialists, 12 surgical residents and 12 surgeons. One interview of a medical specialist was excluded, because the specialist did not have any experience with pharmacists' interventions in our hospital. Characteristics of the physicians are presented in table 3.

**Table 3:** Characteristics of physicians

| | Medical specialties | | Surgical specialties | |
|---|---|---|---|---|
| | **Residents (n=12)** | **Specialists (n=11)** | **Residents (n=12)** | **Specialists (n=12)** |
| Gender | | | | |
| Male | 5 (41.7) | 5 (45.5) | 7 (58.3) | 12 (100) |
| Female | 7 (58.3) | 6 (54.5) | 5 (41.7) | 0 (0) |
| Medical Specialty | | | | |
| Internal medicine | 5 (41.7) | 2 (18.2) | | |
| Neurology | 4 (33.3) | 4 (36.4) | | |
| Cardiology | 3 (25.0) | 2 (18.2) | | |
| Pulmonology | 0 (0) | 2 (18.2) | | |
| Gastroenterology and hepatology | 0 (0) | 1 (9.1) | | |
| General surgery | | | 5 (41.7) | 8 (66.7) |
| Orthopedic surgery | | | 3 (25.0) | 3 (25.0) |
| Neurosurgery | | | 2 (16.7) | 1 (8.3) |
| Plastic surgery | | | 2 (16.7) | 0 (0) |

## Self-reported acceptance rate

In total 41 physicians estimated their own acceptance rate. Some physicians, mostly specialists, did not answer to this question, because they had too little experience with the pharmacist interventions themselves. Mean self-reported acceptance rate was 88.3%

(95% confidence interval (CI) 83.9-92.7). Details are presented in table 4. The reported acceptance rate differed statistically significantly between medical physicians and surgical physicians (81.3% versus 96.4%, p<0.001), but not between residents and specialists (89.6% versus 86.6%, p=0.718).

**Table 4:** Physicians' experiences on pharmacists' interventions

| | Medical specialties | | Surgical specialties | | |
|---|---|---|---|---|---|
| | Residents (n=12) | Specialists (n=11) | Residents (n=12) | Specialists (n=12) | Total (n=47) |
| Self-reported acceptance rate (mean, 95% CI) | 82.9 (74.0-91.9) | 79.3 (67.4-91.2)[c] | 96.9 (94.3-99.6)[c] | 95.6 (88.8-102.5)[d] | 88.3 (83.9-92.7) |
| Number of physicians with a positive opinion (n, %) | | | | | |
| Pharmacists' interventions in general[e] | 12 (100) | 7[a] (63.6) | 12 (100) | 7[b] (58.3) | 38 (80.9) |
| Relevance of interventions[e] | 12 (100) | 9[c] (81.8) | 12 (100) | 7[b] (58.3) | 40 (85.1) |
| Clearness of interventions[f] | 11 (100) | 10[c] (90.9) | 11[c] (91.7) | 7[b] (58.3) | 39 (83.0) |
| Feasibility of interventions[g] | 11[c] (91.7) | 10[c] (90.9) | 10[c] (83.3) | 7[b] (58.3) | 38 (80.9) |

[a] Two physicians in this group could not answer this question
[b] Five physicians in this group could not answer this question
[c] One physician in this group could not answer this question
[d] Four physicians in this group could not answer this question
[e] One medical specialist responded negatively and one medical specialist had a neutral opinion
[f] One medical resident responded negatively
[g] One surgical resident responded negatively

## Barriers and facilitators

Thirty-three physicians reported one or more barriers, resulting in 47 barriers. In total 40 facilitators for acceptance were mentioned by 36 physicians. Two barriers and two facilitators were excluded from analysis, since they were not interpretable.

Medical physicians reported more barriers and facilitators than surgical physicians: 34 versus 11 barriers and 24 versus 14 barriers. Most barriers reported (n=37) were related to physicians' attitude, with inapplicability to the individual patient (n=20) and lack of motivation due to habit and routines (n=8) as most frequently reported barriers. Facilitators were mostly related to physicians' attitude as well (n=28), including confidence in the pharmacist (n=16), followed by the level of knowledge (n=7). Details on barriers, facilitators and illustrative examples are presented in table 5.

## Opinion on pharmacists' interventions

Some physicians, mainly attending specialists, couldn't give their opinion on pharmacists' interventions, because they had too little experience themselves. In total 38 of 47 physicians (80.9%) had a positive general opinion on the interventions. Forty physicians (85.1%) confirmed that the interventions are relevant; 39 physicians (83.0%) confirmed that the interventions are clear and 38 (80.9%) of the physicians found the interventions feasible. On each question only one physician responded negatively. Details on physicians' opinions on pharmacists' interventions are shown in table 4.

**Table 5:** Physicians' barriers and facilitators for acceptance of pharmacist interventions

| | Barrier | M-R | M-S | S-R | S | Total |
|---|---|---|---|---|---|---|
| Attitude | Lack of agreement with interpretation of evidence | 3 | 2 | 0 | 0 | 5 |
| | Examples:<br>"I have a different opinion"(M-R)<br>"The interaction is not clinically relevant (to me)" (M-S) | | | | | |
| | Inapplicable to patient | 7 | 8 | 3 | 2 | 20 |
| | Examples:<br>"There are no other options "(M-S)<br>"I do not agree with the recommendation, because the pharmacist doesn't know the clinically condition."(M-S) | | | | | |
| | Not practical | 1 | 0 | 0 | 0 | 1 |
| | Physician believes that recommendation will not lead to desired outcome | 1 | 1 | 0 | 0 | 2 |
| | Example:<br>"(I decline recommendations when they result in) suboptimal treatment" (M-R) | | | | | |
| | Physician believes he/she cannot perform the recommendation | 1 | 0 | 0 | 0 | 1 |
| | Habit/Routines | 1 | 5 | 2 | 0 | 8 |
| | Example:<br>"I have knowledge on the drug I prescribe"(M-S)<br>"I have experience with certain drug-drug interactions" (M-S) | | | | | |
| Behavior | Intervention characteristics | 4 | 0 | 0 | 0 | 4 |
| | Example:<br>"(I decline recommendations) when the recommendations are not strict" (M-R)<br>"(I decline recommendations for) drug dosing in renal failure" (M-R) | | | | | |
| | Presence of contradictory recommendations | 0 | 0 | 3 | 0 | 3 |
| | Example:<br>"(I decline a) recommendation for an anti-infective agent that is conflicting with the microbiologists' advice" (S-R) | | | | | |
| | Organizational constraints | 0 | 0 | 1 | 0 | 1 |
| | Total | 18 | 16 | 9 | 2 | 45 |
| | **Facilitator** | | | | | |
| Knowledge | Familiarity or aware of own lack of familiarity | 0 | 1 | 0 | 0 | 1 |
| | Awareness or aware of own lack of knowledge | 3 | 2 | 1 | 0 | 6 |
| | Examples:<br>"(I accept interventions) for relevant problems I wasn't aware of" (M-S)<br>"Our lack of knowledge is a reason to accept interventions" (S-R) | | | | | |
| Attitude | Agreement with interpretation of evidence | 2 | 5 | 1 | 0 | 8 |
| | Examples:<br>"(I accept interventions) when the pharmacists holds strong argumentation" (M-S)<br>"(I accepted interventions) when my prescriptions differ from guidelines" (M-S)<br>"(I accept interventions) for relevant interactions that are clinically relevant" (M-R) | | | | | |
| | Applicable to patient | 1 | 0 | 0 | 0 | 1 |
| | Confidence in pharmacist | 5 | 1 | 6 | 4 | 16 |
| | Example:<br>"You (the pharmacists) are the experts" (M-R, M-S, S)<br>"You (the pharmacists) have more knowledge" (M-R, M-S, S-R, S) | | | | | |
| | Practical | 1 | 0 | 0 | 0 | 1 |
| | Physician believes that intervention will lead to desired outcome | 0 | 1 | 0 | 0 | 1 |
| | Not hampered by habit/routines | 0 | 1 | 0 | 0 | 1 |
| | Example:<br>"I don't have experience that differs from the recommendation" (M-S) | | | | | |
| Behavior | Intervention characteristics | 1 | 0 | 1 | 1 | 3 |
| | Example:<br>"(I accept interventions for) drug-drug interactions with risk of QT-prolongation" (M-R) | | | | | |
| | Total | 13 | 11 | 9 | 5 | 38 |

Abbreviations: M-R Medical resident; M-S Medical specialist; S-R Surgical resident; S Surgical specialist
Text between brackets was added by the author to clarify the statements.

## DISCUSSION

Physicians estimated their own acceptance rate of pharmacists' interventions at 88.3% in this study. This self-reported acceptance rate was significantly higher for surgical physicians compared to medical physicians, but there were no differences between residents and specialists.

The self-reported acceptance rate we found is comparable to actual established acceptance rates in previous studies, and some studies indeed showed differences in acceptance rates between different medical specialties.[3, 15] The differences between surgical and medical physicians could probably be explained by the differences in nature of their professions. Medical physicians could have more knowledge on pharmacotherapy as well as wider experience with prescribing.[23] This could result in a more balanced risk-benefit analysis for their patients. Indeed medical physicians mentioned the inapplicability of a recommendation for their patient and their own habit and routines more often as a barrier than surgical specialists. On the other hand, surgical physicians focus on surgical interventions and rarely initiate drugs outside their area of expertise.[23] As a result, they might easier accept a pharmacists' intervention for these drugs, relying on the expertise of the pharmacist.

We had expected to find a difference between residents and specialists, since residents often are not independent decision makers, which has been identified as a barrier for adherence to antimicrobial guidelines.[24] In our study residents reported an acceptance rate comparable to the acceptance rate of their supervisors, possibly because supervisors trained their residents how to deal with pharmacists' interventions.

Most reported barriers for acceptance of interventions were related to physicians' attitude. The most frequently reported barriers, inapplicability to the patient and inertia to previous practice, stress the importance of an assessment of the clinical relevance for the individual patient by the pharmacists and knowledge on local protocols.

In a previous study on non-adherence to non-steroidal anti-inflammatory drug guidelines, limited applicability to a specific patient and inertia to previous practice were important barriers as well.[17] The model of Cabana et al. has also been used in a study on health care professionals' barriers to optimal antibiotic treatment for community-acquired pneumonia in hospitals.[18] Again, inapplicability to the patient was frequently mentioned as a barrier for non-adherence to guidelines on prescribing empirical antibiotic regimens. Habit and routines were also mentioned, but these were not the most important barriers. However, more barriers on the level of knowledge were reported, with lack of awareness being the main barrier for dosage adjustments in renal failure. Besides, social context, such as social pressure, was an important barrier for adherence to almost all specific recommendations, including prescribing empirical antibiotic regimens, timely initiation of

therapy and switching therapy from intravenous to oral. These barriers were less important in our study. However, when physicians consider an intervention as not applicable to their patient, this may be partly caused by a lack of awareness or other barriers influencing their behavior.

Reported facilitators were mostly related to physicians' attitude as well, with confidence in the expertise and knowledge of the pharmacist reported most frequently. Almost all physicians had a positive general opinion on pharmacists' interventions and more specific about the relevance, clearness and feasibility of the interventions. Apparently, pharmacists in our hospital clearly showed their knowledge and expertise and gained confidence from physicians.

Our study has some limitations. First, we used short questionnaires, whereas semi-structured in-depth interviews would yield more detailed information on physicians' barriers and facilitators. For example, when physicians mention inapplicability to their patient as reason for non-acceptance, this may in fact be due to a lack of awareness, inertia to previous practice or social pressure. Second, we made notes during the interviews, where it would have been better to audiotape the interviews to be able to transcribe physicians' answers verbatim. Third, it is possible that physicians gave professionally or socially acceptable answers. For example, physicians' barriers and facilitators may be different in real practice. Fourth, since barriers and facilitators probably differ between settings, our results cannot be extrapolated as such to other settings.[16]

Still, our study is one of the first to explore barriers and facilitators for accepting pharmacists' interventions in general. In order to get detailed information on these barriers and facilitators, a prospective study is recommended, using in-depth semi-structured interviews by an independent interviewer on physicians' argumentation to accept or decline an intervention.

To improve the acceptance rate in routine clinical practice, the identified barriers should be addressed. Therefore, we recommend integrating specialized pharmacists in the medical team on the ward, which could probably result in a more accurate assessment of the clinical relevance of a potential drug-related problem for an individual patient, taking into account habits and routines on the ward. The finding that confidence in the knowledge and expertise of the pharmacist was the main facilitator for acceptance seems a good starting point for this integration, especially on surgical wards. Physicians' confidence in the knowledge of the pharmacists also stresses the importance of continuing education of clinical pharmacists, to maintain and update their professional knowledge.

Based on the results of our study, we conclude that most physicians are positive about pharmacists' interventions in general and that they intend to accept the majority of interventions. Most barriers and facilitators for acceptance were related to physicians' attitude, with inapplicability for the individual patient as most important barrier and confidence in the pharmacist as most important facilitator for acceptance. Apparently, pharmacists gained this confidence from physicians by clearly demonstrating their expertise. To optimize physicians' acceptance rate with the ultimate goal to improve pharmacotherapy, physicians' main barriers and facilitators need to be addressed by clinical pharmacists.

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# 9

## Summarizing Discussion

During drug treatment, which is an essential aspect of medical treatment, drug-related problems occur frequently in hospitalized patients.[1] These drug-related problems include both medication errors and adverse drug events. Adverse drug events, in turn, are divided into preventable adverse drug events, i.e. patient harm caused by medication errors, and adverse drug reactions, caused by the intrinsic toxicity of drugs during normal use.

Previous studies identified numerous risk factors for drug-related problems on the level of the organization, the patient and the specific drug. This contributed to the identification of specific patients groups at risk of drug-related problems, such as patients with renal failure. However, an overall risk stratification approach or prediction model to identify patients with a high probability of developing drug-related problems still needs to be developed. Since it would be efficient for clinical pharmacists to target their efforts to these high-risk patients and to detect adverse drug events in an early stage, additional studies on these topics are presented in this thesis.

Individuals with an intellectual disability may be especially at risk for drug-related problems, since a number of risk factors, including polypharmacy, extensive use of drugs acting on the central nervous system and impaired cognition are pertinent in this population. However, the scope of these problems and interventions to reduce them are largely unknown in this population. Our studies in these vulnerable patients are among the first studies addressing these issues.

The absence of a risk stratification approach partly explains why studied interventions to reduce drug-related problems are mainly targeted at the organizational level. These interventions include optimization of the pharmaceutical care process by implementing computerized physician order entry in combination with (advanced) clinical decision support (CPOE/CDSS), integrating clinical pharmacists in medical teams and performing medication reconciliation and medication reviews. Whereas a combination of these strategies is operated in daily clinical practice, the evidence on the effect of them is usually derived from single intervention studies. Therefore, we compared the detection of drug-related problems by medication review with computerized alerts, generated by CPOE/CDSS in a setting where both interventions are combined.

Both CPOE/CDSS and medication review result in the detection of drug-related problems for individual patients, followed by recommendations to the responsible physician to resolve these problems. To optimize the effect of these interventions on quality of patient care, detailed knowledge on physicians' acceptance rate of these interventions is important. The studies presented in part II of this thesis contribute to this knowledge.

The main objectives of this thesis were to identify determinants for medication errors and patients at risk for adverse drug events (part I) and to evaluate the effect of clinical

pharmacists' interventions to optimize pharmacotherapy (part II) in both hospitalized patients and individuals with an intellectual disability.

Part I of this thesis focused on identifying determinants for medication errors and patients at risk for adverse drug events. We showed that in hospitalized patients medication errors resulting in preventable adverse drug events and medication errors without patient harm have some determinants in common, namely hospital, ward and anti-infective agents (chapter 2). This indicates that these drug-related problems share the same origin to some extent, mainly at the organizational level, justifying organizational interventions to reduce medication errors and subsequent adverse drug events.

In older individuals with an intellectual disability we found a prevalence of prescribing errors of 47.5%. Higher age, less severe intellectual disability, higher body mass index (BMI), higher frailty index, polypharmacy and drugs acting on the central nervous system were identified as determinants for these errors (chapter 3).

We did not find an association between adverse drug events and the number of biochemical tests performed before the occurrence of adverse drug events (chapter 4), so the number of biochemical tests cannot be used as an alert to detect adverse drug events before they become manifest.

In part II of this thesis the effect of clinical pharmacists' interventions to optimize pharmacotherapy in both hospitalized patients and individuals with an intellectual disability was evaluated.

First, we showed that weekly medication review in hospitalized patients performed by a clinical pharmacist followed by a discussion with the treating physician on the ward, results in the detection of clinically relevant drug-related problems in hospitalized patients, of which only 8% are identified by CPOE/CDSS (chapter 5). In addition, CPOE/CDSS generates a significant number of irrelevant alerts.

Our pilot study in adults with an intellectual disability demonstrated that structured medication review could be used to identify drug-related problems in this specific population (chapter 6). Drug-related problems were identified in all included adults (n=27), but the actual implementation of recommendations to resolve drug-related problems by physicians was only 15.7%.

This is in contrast with the acceptance rate of 71.2%, which we found for pharmacists' interventions in hospitalized patients, based on CPOE/CDSS alerts and a clinical rule for dosing in renal failure. The probability for acceptance increases for patients with an increasing number of medication orders and for clinically relevant problems. Interventions regarding continued pre-admission treatment were less likely to be accepted (chapter 7). Our exploration of physicians' barriers and facilitators for acceptance of pharmacists' interventions (chapter 8) showed that both are mainly related to physicians' attitude. Inap-

plicability of the intervention to the individual patient was the most frequent mentioned barrier, whereas confidence in the pharmacist, which they gained by clearly demonstrating their expertise and knowledge, was the main facilitator for acceptance.

In this final chapter our main results are critically reviewed in a wider perspective in relation to the main objectives of this thesis.

## DRUG-RELATED PROBLEMS: DEFINITIONS AND STUDY METHODS

In medication safety literature, different definitions for the different types of drug-related problems and their mutual relationship are being used, which complicates comparison of results between studies. In 2005 Yu et al. found as much as 119 different definitions for 25 safety terms, including 11 definitions for adverse drug reactions, 10 definitions for adverse drug events and 7 for medication errors, on websites of organizations involved in medication safety. These definitions were not only worded differently, but also had different functional meanings.[2] For example, we used the term medication error for all errors in the medication process, irrespective of their outcome whereas others referred to incidents without harm or errors that were intercepted before reaching the patient as "near misses".

The assessment of the causal association between drug treatment and patient harm is a second issue in research on adverse drug events, since it shows high inter-rater variability, even among experts in pharmacovigilance.[3, 4] Methods that are being used for causality assessment are generally based on probabilistic theories derived from Bayes' theorem, algorithms or expert judgment.[5] However, these methods, including the Yale algorithm we used in our studies, are designed for pharmacovigilance and focus on adverse drug reactions.[6] Therefore, we previously developed an algorithm, based on the simplified Yale algorithm, for the structured assessment of the association between medication errors and preventable adverse drug events, including the (potential) severity of the error.[7] However, agreement between pharmacists and physicians on the presence of preventable adverse drug events and the severity of these events was only fair to moderate. And even more striking, physicians did not regard almost one third of the errors identified by pharmacists as errors at all. We hypothesized before, that physicians may assess errors from a different perspective given their profession, looking at the patient and his current condition first, followed by an assessment of the clinical relevance of an error, whereas pharmacists are focused on the drug and the medication process itself.[7]

Due to such differences between professionals, causality assessment should be a consensual process, in which both physicians and pharmacists are involved, in particular for research purposes. In daily clinical practice (potentially) relevant drug-related problems

are usually discussed with a physician, who can decide to accept or decline a recommendation for an individual patient, as we showed in part II of this thesis.

Third, the method of data collection influences the detection of drug-related problems. For example, spontaneous reporting is prone to under-reporting and biased reporting. To cover all prescribing errors, including those that did not result in patient harm, a process-based approach is recommended, for example by reviewing medication orders, retrospectively or prospectively.[8] The clinical context of a patient, such as renal function and other comorbid conditions should always be taken into account for an accurate detection of errors. For example, a drug-drug interaction that is well managed in an individual patient by measuring biochemical parameters or serum drug levels should not be considered as a prescribing error.

Detecting adverse drug events usually requires an outcome-based approach, such as more intensive and time-consuming chart review. Computerized trigger tools might be more efficient in identifying adverse drug events. However, Jha et al. showed that chart review detects more events than computerized monitoring and that the overlap between the methods was very small; only 12% of detected adverse drug events were identified by both methods.[9]

As a result of these different data collection methods for medication errors and adverse drug events, the information on drug-related problems is fragmented, since most studies focused either on medication errors and estimated subsequent harm (without actually assessing the actual occurrence of harm), or on adverse drug events with an assessment on the preventability of the events. To get a complete picture of drug-related problems, all these events should be studied together, using a combination of process-based data collection methods with outcome-based data collection methods, in prospective multicenter studies, preferably on a national level.

Given these difficulties in medication safety research, reported rates for the different types of drug-related problems vary to a substantial degree.[1, 10] It seems evident that clear and unambiguous definitions, reliable causality assessment and a uniform combination of process-based and outcome-based data collection methods is needed. This may seem unrealistic, given the fact that several definitions and classifications have been proposed[11-13] that have not been uniformly adopted in patient safety research yet. Even in this thesis, we used different classifications for drug-related problems. In chapters 2 and 3, focusing on prescribing and transcribing errors, we used a process-based classification, whereas in chapter 5 and 7 we used a broader classification for both errors and adverse drug events.

The terminology, causality assessment and taxonomy of adverse drug reactions of the World Health Organization (WHO)[14] is being applied worldwide in the field of pharmacovigilance, from clinical trials to drug registration and post-marketing surveillance. Therefore, we believe that a comparable framework could work for drug-related problems as well. This framework could build on WHO's adverse drug reaction taxonomy, expanded

with a definition and classification for medication errors and a procedure for assessing the causal relationship between a medication error and preventable adverse drug events, as we used in chapter 2 and 4.

## PATIENTS AT RISK FOR ADVERSE DRUG EVENTS

As stated before, a comprehensive approach to identify high-risk patients in hospitals and target interventions to these patients has not been developed yet. This may be explained by several factors.

First, age and the number of drugs (or polypharmacy) have been most frequently associated with the occurrence of drug-related problems.[1, 10, 15] Since a large proportion of hospitalized patients are older than 65 years and use more than five drugs, these risk factors are too unspecific for an effective risk stratification approach in hospitalized patients.

Second, the number of comorbid conditions has been frequently identified as a risk factor as well.[16-18] This information is mainly recorded as free text in the electronic medical patient record, in particular in hospitalized patients. As a result, it is complicated to use this information to detect high-risk patients. For the same reason, we could not address the number of comorbid conditions in our studies. When this information would be coded in the electronic medical patient record, comparable to the documentation of diseases and intolerances by general practitioners and community pharmacists[19], it would be easier to use in daily clinical practice, for clinical rules and for research purposes.

Third, it is possible that the studied risk factors are not specific enough to identify patients that will develop adverse drug events. Almost fifteen years ago, Bates et al. tried to develop a patient risk stratification strategy. They concluded that adverse drug events occur relatively randomly across hospitalized patients and that preventable adverse drug events are mostly the result of organizational problems.[20] Possibly, a combination of single risk factors into one prediction model could increase the specificity to identify patients at risk.

To develop such a prediction model, lessons could be learned from the development of early warning scores, designed to identify hospitalized patients at risk of sudden cardiac arrest or transfer to an intensive care unit (ICU) using vital signs (e.g. blood pressure, heart rate, temperature, oxygen saturation, respiratory rate and level of consciousness). In a recent review, it was demonstrated that aggregate weighted scoring systems have the highest accuracy to predict cardiac arrest, ICU transfers and mortality.[21] These aggregated scoring systems categorize parameters into different degrees, and assign point values for the different categories, that are summed to obtain the total risk score. The variables used in such a score should be easily available from the electronic medical patient record or medication records and could include among others ward type, presence of renal failure

and certain pharmacotherapeutic groups. Subsequently, the accuracy (sensitivity and specificity) of the tool needs to be determined and eventually the validated tool should preferably be completely automated and integrated in the electronic medical record.

## INDIVIDUALS WITH AN INTELLECTUAL DISABILITY: A POPULATION AT RISK

The studies we performed in individuals with an intellectual disability are among the first studies on drug-related problems in this population. Given the risk factors pertinent in this population, it is not surprising that we found a high prevalence of drug-related problems, often related to drugs acting on the central nervous system.

The evidence of the contribution of pharmacists to patient care in this population is scarce.[22] This "absence of evidence" is probably not "evidence of absence" of pharmacists' services in this population, as Bell et al. stated in their editorial on this topic.[23] However, practice-based research on potentially effective interventions to reduce drug-related problems in these vulnerable patients needs to be encouraged. Structured medication review is one of these possible interventions, but a tool needs to be designed to detect drug-related problems that are common in this population, including a risk-benefit analysis of psychotropic drugs and the possibility of withdrawal of unnecessary drugs. Furthermore, research is necessary to explore means to involve individuals with an intellectual disability in the identification of drug-related problems during structured medication review. Although these patients have shown to have less understanding of their drug therapy, almost all patients included in a descriptive study said they wanted an understandable leaflet with information on their drugs, which should include the indication and side effects.[43] Physicians and pharmacists could compose these leaflets together to inform clients on pharmacotherapy in an understandable manner, such as Unwin and Deb did in the UK.[44]

## OPTIMIZING PHARMACY SERVICES TO REDUCE DRUG-RELATED PROBLEMS

We showed that a clinical pharmacist can detect drug-related problems in addition to basic CDSS (chapter 5). A number of these drug-related problems, identified by medication review, could be detected by more advanced clinical decision support, as presented in table 1. Actually, the same holds for the START/STOPP-criteria used in the structured medication review in individuals with an intellectual disability (chapter 6). Integrating these problems into CPOE/CDSS could also result in earlier detection of the problems,

**Table 1:** Detecting drug-related problems using advanced clinical decision support

| Class | Subclass | Advanced CDSS possible? | System requirements |
|---|---|---|---|
| Indication | Additional drug therapy required | Partly | For drug therapy indicated to prevent adverse drug events: Linking use of a drug with lacking of a drug to prevent adverse drug events.<br>For other START-criteria: Linking a drug to coded information on comorbid conditions or to a drug specific for a comorbid condition (requires coding of all comorbid conditions) |
| | Unnecessary drug therapy | Partly | For STOPP-criteria: Linking a drug to the absence of a specific comorbid condition (requires coding of all comorbid conditions). |
| Effectiveness | Ineffective drug therapy | Partly | Linking of a drug to the reason for prescribing and, where relevant, the duration of therapy.<br>For anti-infective agents drugs: linking to microbiological tests results. |
| | Dosage too low | Yes | Integrated in basic CDSS.<br>Linking to age and body weight could increase the specificity of alerts. |
| Safety | Adverse drug event | Partly | Linking abnormal biochemical results with certain drugs.<br>Linking initiation of an antidote to use of a drug.<br>Linking initiation of a drug to treat an adverse drug event (misinterpreted as a new condition, i.e. the prescribing cascade) to use of a drug. |
| | Dosage too high | Yes | Integrated in basic CDSS.<br>For dose-checking in renal failure: Linking to laboratory results.<br>Linking to age and body weight would increase the specificity of alerts, especially in pediatric and older patients. |
| Drug use | Drug use problem | Partly | Information of the patient is required to detect these problems.<br>Use of an enteral feeding tube, documented as coded information, could be detected by CDSS. |
| Pharmaceutical care | Monitoring | Partly | Linking test results, such as biochemical parameters, electrocardiogram recordings, blood pressure measurements, to initiation and use of a drug. |
| | Drug-drug interaction | Yes | Integrated in basic CDSS.<br>Linking with laboratory results and patient characteristics (age) could increase the specificity of alerts. |
| | Contra-indicated drug | Partly | Depending on coded documentation of comorbid conditions, allergies and intolerances in the electronic medical patient record. This includes some STOPP-criteria. |
| | Lifestyle | No | Information of the patient is required to obtain this information |
| | Duplicate therapy | Yes | Integrated in basic CDSS. |
| | Discrepancy with pre-admission pharmacotherapy | Partly | Linking of prescription data between healthcare settings, e.g. a national electronic patient record. |

namely during or immediately after prescribing, leaving room for tailoring pharmacotherapy to patients' preferences during a medication review.[24]

In addition, advanced CDSS can also reduce the number of clinically irrelevant alerts of basic CDSS. As shown by Helmons et al. this can result in a significant reduction of the number of alerts and time spent on checking of alerts for drug-drug interactions.[25]

Still, for other drug-related problems, such as the identification of unnecessary drugs and the detection of certain adverse drug events, a clinical pharmacist integrated in the medical team, who can perform medication reviews, is recommended. This pharmacist could combine the computer-based alerts and additional problems, to prioritize the problems and to compose a pharmaceutical care plan.

Pharmacy services could be optimized further by improving the acceptance rate of pharmacists' interventions for individual patients. Physicians may have valid arguments to neglect pharmacists' recommendations, since prescribing the right drug to the right patients includes balancing the potential benefits and risks of a treatment. Besides, patients' preferences and costs should be taken into account.[26] This implies that pharmacists should include this information, obtained from the physician, nurse and the patient or the electronic medical patient record, in their assessment of the clinical relevance in order to increase the acceptance rate of their advices.

In chapter 5, the acceptance rate of pharmacists' interventions after medication review was only 56%. However, when we look at the interventions that were considered clinically relevant by the physicians, the acceptance rate was 86% (247 of 286 interventions). This indicates that an accurate assessment of the clinical relevance by pharmacists could increase the acceptance rate, which we indeed showed in chapter 7.

The assessment of drug-related problems in daily practice usually requires detailed information on a patients' medical history and current conditions and thus depends largely on the available documentation in the electronic medical record. As a result, it can be time-consuming to retrieve the required information from these records. During the study described in chapter 5, we learned that it is more efficient to discuss the identified potential drug-related problems with the attending physician, explaining the relatively large number of irrelevant alerts. However, an increasing number of irrelevant interventions could compromise physicians' confidence in the knowledge and skills of pharmacists.

Besides, most drug-related problems in the study presented in chapter 5 were potentially unnecessary drugs. Recommendations to withdraw a drug could be more difficult to accept, especially regarding medication initiated before admission by another physician. This is supported by our finding in chapter 7 that interventions regarding medication initiated before admission are less likely to be accepted. This was confirmed in a recent study by Poots et al, showing that junior doctors find it difficult to stop medication during a medication review at hospital admission and considered it as a responsibility of the

general practitioner or certified specialist.[27] Remarkably, physicians did not report that they believed they were unable to change medication initiated by another physician at all in our study (chapter 8). Apparently this is not the first barrier that crosses their minds.

## CASE MANAGEMENT

The difficulties with medication initiated before admission raise the question who is responsible for chronic pharmacotherapy in patients treated by more than one physician. Therefore, every patient needs a case manager, regularly reviewing all pharmacotherapy. In primary care, the general practitioner fulfills this role and in organizations for individuals with an intellectual disability, the physician specialized for individuals with an intellectual disability is this case manager. Medication reviews should be performed by the designated case manager in close collaboration with the patients' pharmacists. During hospital admission, clinical pharmacists integrated in the medical team, could partly fulfill the role of pharmacotherapeutic case manager. We suggest that they discuss the most urgent interventions with the responsible resident or attending physician. However, non-urgent interventions could be discussed with the designated case manager in primary care. Of course, in all settings prescribers who initiated the therapy should be consulted when necessary and should be informed about any changes in therapy.

## CROSSING BARRIERS TO REDUCE DRUG-RELATED PROBLEMS: PHARMACIST PRESCRIBING

Physicians' most important facilitator for actually accepting pharmacists' interventions is their confidence in the knowledge and skills of the pharmacists. The desire to make greater use of these skills and specialization of pharmacists was the main argument for authorizing pharmacists for prescribing in the United Kingdom.[28] Therefore, the confidence of physicians could be a good starting point for exploring pharmacist prescribing in the Netherlands, which could partly cross the barriers of physicians' acceptance, including the reluctance of physicians to change medication initiated by another physician. In addition, it could be seen as a natural extension of the pharmacist's role in advising physicians in good prescribing.

Pharmacist prescribing is currently allowed in Canada, the United States and the United Kingdom (UK).[29] Since most experience with pharmacist prescribing is reported from the UK, we will discuss the two British models for pharmacist prescribing, supplementary prescribing and independent prescribing, in more detail.

Pharmacist supplementary prescribing (or dependent prescribing) was permitted in the UK since 2003. Supplementary prescribing is defined as "a voluntary partnership between the responsible independent prescriber (a physician or a dentist) and a supplementary prescriber, to implement an agreed patient specific clinical management plan with the patient's agreement particularly, but not only, in relation to prescribing for a specific non-acute medical condition or health need affecting the patient."[28] The clinical management plan must mention the pharmacotherapeutic groups that may be prescribed by the pharmacist. To acquire prescribing rights a course needs to be completed, which includes a period of learning in practice, supervised by a mentor, who is usually the independent prescriber with whom the dependent prescriber will form a prescribing relationship.[29]

Subsequently, independent prescribing was introduced in 2006. An independent prescriber is defined as a practitioner responsible for the assessment of patients with undiagnosed or diagnosed conditions and for decisions about the clinical management required, including prescribing.[28]

In their review on prescribing pharmacist activities in the UK, published in 2007, Tonna et al. state that especially the practice of hospital pharmacists, who are part of a multidisciplinary patient team and have access to medical records, lends itself for pharmacist prescribing. However, the impact of pharmacist prescribing on the quality of patient care has not been well established.[28]

Especially within specific protocols pharmacist prescribing could be useful, for example: dosage adjustments based on therapeutic drug monitoring, dosage adjustments in patients with renal failure, clinical nutrition, medication reconciliation, discharge planning and adherence to guidelines.[30-32]

Barriers for implementing pharmacist prescribing were identified in different studies and included financial and organizational problems, general lack of awareness of the pharmacists role, and fear of pharmacists' vulnerability to conflicts of interests with pharmaceutical companies.[28, 29, 33] These barriers need to be addressed before implementing pharmacist prescribing. For example, prescribing pharmacists should not be involved in drug purchasing and negotiations with companies to prevent conflicts of interests.

Besides, medical staff members expressed their concerns on pharmacists' limited patient contact and limited diagnostic skills, compared to nurses, to ensure safe prescribing.[28] This is an important concern, especially in Dutch hospital settings, where the integration of clinical pharmacists on the wards is progressing slowly. On the other hand, a recent study in the UK showed that prescribing error rates for pharmacist prescribers did not significantly differ from certified specialists.[34]

In the Netherlands, prescribing is a reserved act for physicians, dentists and midwives. Since 2014, nurse practitioners and physician assistants are authorized to prescribe low risk medication, within their field of expertise and according to current guidelines. This model could be extended to clinical pharmacists. There are some examples from

the Netherlands, where pharmacists already have a role in continuing medication in the medication reconciliation process at admission and prescribing upon discharge, actually acting as dependent prescribers.[30-32]

However, to ensure safe prescribing detailed knowledge on the patient, his current conditions and medical history and his preferences are essential. Besides, to be able to prescribe in concordance with the patient, patient contact is required. Therefore, additional training in communication with patients, clinical judgment and decision making would be required. Last but not least, patients' perspectives on pharmacist prescribing need to be taken into account.

## EFFECTS OF INTERVENTIONS ON MORBIDITY, MORTALITY AND HEALTHCARE COSTS

Although, improving clinical pharmacy services can result in the detection and reduction of drug-related problems and is likely to benefit the patients, the impact on clinically relevant end points, including morbidity, hospitalizations and mortality, as well as the cost-effectiveness has not been unambiguously demonstrated.

For example, integrating pharmacists in the medical team on hospital wards did result in shorter length of stay and a reduction in costs in some studies.[35] However, in a recent Dutch multicenter randomized trial, the effect of a ward-based pharmacy team, performing medication reconciliation and regular medication reviews, did not result in a reduction of length of stay and number of complications in surgical patients.[36] Actually the same holds for medication review, of which the effect on mortality and hospital admissions in both hospitalized patients and primary care setting remain uncertain.[37, 38]

To give some possible explanations for these conflicting results we would like to refer to the gold standard to show the efficacy of a new drug: comparison of the new drug to the current standard of care in double-blind controlled randomized trials. In our field of research, blinding patients and healthcare professionals to pharmacists' interventions is impossible, which could lead to bias in the interpretation of the results of performed studies. Randomization on the level of wards or hospitals, in case of multicenter studies, is possible. However, differences in settings, such as the CPOE/CDSS used, could interfere with the studied intervention. This is why pre-post interventions designs are often used. However, this method has its own limitation, namely that other changes in the care process or the introduction of new treatments could influence the outcomes.

More important, patients included in drug-efficacy trials need to comply with strict inclusion criteria to obtain a homogeneous sample and the study protocol controls all important variables so only the intervention can impact the outcomes. However, pharmacists' interventions, which are heterogeneous themselves, are targeted to a heterogeneous

population, since for example age, the current condition, comorbid conditions and drug use differs between patients. And, although pharmacotherapy is an important part of medical treatment, patients undergo many other types of interventions, especially during hospital admissions, such as surgery or renal replacement therapy, that probably have a larger impact on morbidity and mortality than pharmacists' interventions to optimize pharmacotherapy.

## OTHER INTERVENTIONS TO REDUCE DRUG-RELATED PROBLEMS

In this thesis we focused on improving clinical pharmacy services to optimize pharmacotherapy. In addition, other organizational measures and national policies could contribute to reduction of drug-related problems. Some examples will be discussed briefly below.

### Patient participation in medication safety

Involving patients and their relatives in their own safety could contribute to reduce drug-related problems and optimize pharmacotherapy, since they are the one constant factor within the entire care process. This requires patient empowerment, defined as the process by which patients gain more control over their health and health care.[39] Empowered patients understand their health conditions and the need for lifestyle changes, can participate in decision-making, can make informed choices, are able to ask questions, take their responsibility for their health and make use of available information.[40]

For involvement in patient safety, patients should at least be aware of their responsibility to keep track of their current pharmacotherapy, history of allergies and experienced adverse drug reactions. This is especially important for medication reconciliation at transitions between care settings, to which patients can add essential information.[41]

Besides, patients should be made aware that they should ask questions whenever they have doubts on their medication, such as dose omissions or discrepancies with pre-admission treatment during hospitalization. Clinical pharmacists could play a role in supporting patients to ask questions on their pharmacotherapy.[42]

### Education of healthcare professionals

Since lack of information on drugs, insufficient pharmacological knowledge and insufficient training are identified as risk factors for medication errors and preventable adverse drug events, education of healthcare professionals on good prescribing and reducing drug-related problems is extremely important. [1, 45 46 47, 48] Recently, Ashcroft et al. showed that error rates are higher for all physicians during their post-graduate or specialty training program compared to certified specialists. On the other hand, certified specialists made more serious prescribing errors.[34] Therefore, undergraduate education, postgraduate training

and continuous professional development is required to improve prescribing skills. First, practical prescribing skills need to be assessed before graduating, comparable to the UK, where a national assessment of prescribing competence has been introduced for all students.[49] After graduation, academic detailing (face-to-face education by trained healthcare professionals) has been shown to have a positive effect on the quality of prescribing.[50, 51] In addition, formally discussing and providing constructive feedback on errors can improve learning from these errors.[52] Clinical pharmacists, integrated in medical teams, could play a role in this continuing education of physicians and nurses.

Physicians referred to clinical pharmacists as experts in knowledge on drugs and the medication process our study. However, the postgraduate residency program for clinical pharmacists in the Netherlands should focus more on the patient and collaboration with other professionals to improve their clinical skills.

Summarizing, our results show that it is difficult to select patients at risk of adverse drug events, but there are opportunities for clinical pharmacists to improve their services to detect drug-related problems and improve pharmacotherapy. This leads us to the following recommendation for patient care.

## RECOMMENDATIONS FOR PATIENT CARE

To optimize pharmacotherapy in daily patient care, we have the following recommendations:

- Clinical decision support and clinical rules should be optimized to detect drug-related problems and to reduce the number of irrelevant alerts.

- Clinical pharmacists should be integrated with medical teams to focus on drug-related problems and adverse drug events in particular, using medication review, in both hospitalized patients and individuals with an intellectual disability. These pharmacists could also contribute to patient empowerment and education of physicians and nurses.

- Pharmacists should be aware of physicians' barriers for acceptance of pharmacists' interventions in daily routine, including an accurate assessment of the clinical relevance for the individual patient.

As in all research, our studies leave many questions unanswered which future research should look into.

## RECOMMENDATIONS FOR FUTURE RESEARCH

To solve the remaining issues on drug-related problems and the effects of interventions:

- A taxonomy for drug-related problems, including definitions and assessment methods should be developed and implemented on a worldwide level to obtain comparable results from medication safety studies.

- Studying the effect of interventions to optimize pharmacotherapy in individuals with an intellectual disability, including structured medication review designed to detect common drug-related problems in this vulnerable population, should be stimulated.

- The possibilities for pharmacist prescribing within their field of expertise and according to specific protocols, should be explored.

## CONCLUSIONS

Summarizing, we conclude that it is difficult to detect patients at risk for drug-related problems, especially for adverse drug events. Until better prediction models are developed, interventions to optimize pharmacotherapy should be targeted at the organizational level. These interventions include optimization of computerized physician order entry combined with advanced clinical decision support and integration of pharmacists in the medical team. These pharmacists can perform medication reviews to detect drug-related problems, both in hospitalized patients and individuals with an intellectual disability.

Both computerized physician order entry with clinical decision support and medication review result in patient-specific recommendations to optimize pharmacotherapy. Physicians' acceptance of these interventions could be improved, taking physicians' barriers into account. Extension of pharmacists' role to prescribing pharmacotherapy is an interesting opportunity to optimize pharmacotherapy that should be explored.

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# Samenvatting

Geneesmiddelen zijn onmisbaar bij de behandeling van ziektes, het verlichten van symptomen en het voorkomen van toekomstige complicaties. Behandeling met geneesmiddelen, oftewel farmacotherapie, heeft helaas een keerzijde; er kunnen zogenaamde geneesmiddelgerelateerde problemen optreden. Deze problemen omvatten enerzijds medicatiefouten, die gemaakt worden in het proces van voorschrijven tot toedienen en waarvan naar schatting maximaal 10% tot vermijdbare schade bij de patiënt leidt. Anderzijds kunnen bij juist gebruik van geneesmiddelen bijwerkingen optreden. Deze bijwerkingen en vermijdbare schade worden samen geneesmiddelgerelateerde schade genoemd.

Geneesmiddelgerelateerde problemen komen frequent voor bij patiënten opgenomen in ziekenhuizen. In eerdere onderzoeken zijn verschillende risicofactoren geïdentificeerd voor het optreden van dergelijke problemen. Dit heeft bijgedragen aan de identificatie van patiënten met een verhoogd risico, maar er is nog geen predictiemodel voorhanden om patiënten met het hoogste totale risico te identificeren. Een dergelijk predictiemodel zou apothekers kunnen helpen hun aandacht te richten op patiënten met de meeste kans op geneesmiddelgerelateerde problemen. Daarom hebben wij een aantal aanvullende onderzoeken gedaan naar risicofactoren voor geneesmiddelgerelateerde problemen bij patiënten in het ziekenhuis.

Een aantal risicofactoren voor geneesmiddelgerelateerde problemen, zoals polyfarmacie (het gebruik van vijf of meer geneesmiddelen), een verminderd denkvermogen en het gebruik van geneesmiddelen werkend op het zenuwstelsel, komen frequent voor bij mensen met een verstandelijke beperking. De frequentie van geneesmiddelgerelateerde problemen in deze patiëntengroep is echter niet goed onderzocht en daarom wordt daar in dit proefschrift aandacht aan besteed.

Interventies om geneesmiddelgerelateerde problemen te voorkomen zijn tot op heden voornamelijk gericht op optimalisatie van het medicatieproces. Een voorbeeld daarvan is de implementatie van elektronische voorschrijfsystemen met beslissingsondersteuning. Deze beslissingsondersteuning genereert signalen tijdens het voorschrijven van geneesmiddelen die mogelijk een probleem kunnen zijn bij de betreffende patiënt, bijvoorbeeld in geval van overdosering, een allergie of een wisselwerking met een ander geneesmiddel.

Daarnaast kan het integreren van apothekers in medische behandelteams op verpleegafdelingen en het uitvoeren van medicatiereviews bijdragen aan het detecteren en verminderen van geneesmiddelgerelateerde problemen. Hoewel elektronische voorschrijfsystemen en het integreren van apothekers in behandelteams in de praktijk naast elkaar worden toegepast, is het effect van deze organisatorische maatregelen veelal vastgesteld in onderzoeken gericht op een afzonderlijke maatregel. Daarom hebben wij een onderzoek uitgevoerd om de detectie van geneesmiddelgerelateerde problemen met behulp van medi-

catiereview door een ziekenhuisapotheker, die nauw betrokken is bij het behandelteam, te vergelijken met de automatische signalen afkomstig van beslissingsondersteuning.

Zowel beslissingsondersteuning als medicatiereview resulteert in detectie van geneesmiddelgerelateerde problemen voor individuele patiënten, resulterend in een advies van een apotheker aan de behandelend arts. Om het effect van deze interventies van apothekers te optimaliseren is het van belang om inzicht te krijgen in de mate waarin artsen deze interventies daadwerkelijk accepteren en hun argumentatie daarvoor.

In dit proefschrift richten wij ons op patiënten opgenomen in ziekenhuizen en mensen met een verstandelijke beperking. Ons eerste doel is het identificeren van risicofactoren voor medicatiefouten en patiënten met risico op geneesmiddelgerelateerde schade (deel I). Daarnaast evalueren we interventies van apothekers om farmacotherapie te optimaliseren (deel II).

## DEEL I RISICOFACTOREN VOOR MEDICATIEFOUTEN EN GENEESMIDDELGERELATEERDE SCHADE

In hoofdstuk 2 hebben we aangetoond dat medicatiefouten die niet tot schade leiden en medicatiefouten die resulteren in schade bij opgenomen patiënten een aantal dezelfde risicofactoren hebben, namelijk: het ziekenhuis, de verpleegafdeling en middelen tegen infecties. Dit geeft aan dat deze problemen gedeeltelijk dezelfde oorsprong hebben en rechtvaardigt organisatorische maatregelen voor de reductie van medicatiefouten en schade die daar uit voort kan vloeien.

Bij personen met een verstandelijke beperking hebben we een prevalentie van voorschrijffouten van bijna 48% gevonden (hoofdstuk 3), vergelijkbaar met ouderen in de algemene populatie. Een hogere leeftijd, een minder ernstige verstandelijke beperking, een hogere body mass index, een hogere mate van kwetsbaarheid, gebruik van geneesmiddelen werkend op het zenuwstelsel en polyfarmacie verhogen de kans op voorschrijffouten.

In de dagelijkse praktijk wordt geneesmiddelgerelateerde schade niet altijd herkend. De arts zou wel een vermoeden kunnen hebben dat er iets met de patiënt aan de hand is en dit 'niet-pluisgevoel' leidt doorgaans tot extra diagnostiek. In hoofdstuk 4 hebben we daarom onderzocht of er een verband is tussen het aantal uitgevoerde klinisch chemische bepalingen en het optreden van geneesmiddelgerelateerde schade bij opgenomen patiënten. Wij hebben dit verband niet kunnen aantonen en daarom kan het aantal uitgevoerde bepalingen niet worden gebruikt om geneesmiddelgerelateerde schade vroegtijdig op te sporen.

## DEEL II INTERVENTIES VAN APOTHEKERS OM FARMACOTHERAPIE TE OPTIMALISEREN

In hoofdstuk 5 hebben we laten zien dat apothekers die wekelijks een medicatiereview uitvoeren bij opgenomen patiënten geneesmiddelgerelateerde problemen kunnen identificeren. Slechts 8% van deze problemen wordt door de huidige beslissingsondersteuning gedetecteerd. Bovendien genereert de beslissingsondersteuning meldingen die niet relevant zijn.

Ons pilot-onderzoek bij mensen met een verstandelijke beperking (hoofdstuk 6) laat zien dat een medicatiereview ook bij deze patiënten kan worden gebruikt om geneesmiddelgerelateerde problemen te identificeren. Bij alle 27 onderzochte patiënten vonden wij tenminste één probleem. In dit onderzoek werd niet meer dan 16% van de aanbevelingen ter verbetering van de problemen door de arts geaccepteerd. Dit is waarschijnlijk te verklaren doordat de artsen niet direct bij het review-proces betrokken waren.

Bij opgenomen patiënten blijkt de acceptatiegraad van interventies van apothekers, naar aanleiding van beslissingsondersteuning en een klinische beslisregel voor patiënten met een nierfunctiestoornis, aanzienlijk hoger, namelijk meer dan 70% (hoofdstuk 7). De kans op acceptatie neemt toe bij een toenemend aantal gebruikte geneesmiddelen en is groter voor klinisch relevante problemen. Interventies die betrekking hebben op medicatie die reeds voor opname gebruikt wordt, worden minder snel geaccepteerd. Om meer inzicht te krijgen in de argumenten van artsen om interventies van apothekers al dan niet te accepteren zijn 48 artsen geïnterviewd over dit onderwerp (hoofdstuk 8). Hieruit blijkt dat zowel barrières als faciliterende factoren voor acceptatie gerelateerd zijn aan de attitude van de arts. Het niet van toepassing zijn van een interventie op een individuele patiënt werd het meest genoemd door artsen als reden om een interventie niet te accepteren. Vertrouwen in kennis en kunde van de apotheker was de meest genoemde reden om interventies daadwerkelijk te accepteren. Dit vertrouwen kan dienen als basis voor verdergaande samenwerking tussen artsen en apothekers om geneesmiddelgerelateerde problemen te voorkomen.

## AANBEVELINGEN

Op basis van de resultaten van de onderzoeken in dit proefschrift, hebben wij de volgende aanbevelingen voor de patiëntenzorg:

- Beslissingsondersteuning en klinische beslisregels moeten worden geoptimaliseerd om geneesmiddelgerelateerde problemen te detecteren, met zo min mogelijk irrelevante meldingen.

- Apothekers, met aandacht voor geneesmiddelgerelateerde problemen en bijwerkingen in het bijzonder, moeten meer worden geïntegreerd in medische behandelteams, zowel in ziekenhuizen als instellingen voor mensen met een verstandelijke beperking. Medicatiereview kan daarbij gebruikt worden voor het detecteren van problemen.

- Apothekers moeten zich bewust zijn van de argumenten van artsen om interventies al dan niet te accepteren. Dit betekent onder andere dat de klinische relevantie voor de individuele patiënt goed moet worden ingeschat door de apotheker, voordat de interventie aan de arts wordt voorgelegd.

Natuurlijk roept ons onderzoek nieuwe vragen op en blijven er vragen onbeantwoord, resulterend in de volgende suggesties voor vervolgonderzoek:

- Er moet een wereldwijde taxonomie voor geneesmiddelgerelateerde problemen ontwikkeld worden om resultaten van verschillende onderzoeken te kunnen vergelijken. Deze taxonomie moet de definities van de verschillende begrippen bevatten plus een methode om de relatie tussen schade en een geneesmiddel te kunnen beoordelen.

- Onderzoek naar effectieve interventies om farmacotherapie te optimaliseren bij mensen met een verstandelijke beperking, moet worden gestimuleerd.

- De mogelijkheden voor beperkte voorschrijfbevoegdheid voor apothekers moeten onderzocht worden. Een dergelijke voorschrijfbevoegdheid, vergelijkbaar met de bevoegdheid voor verpleegkundig specialisten en physician assistants, is een logische uitbreiding van de rol van apothekers in het adviseren van voorschrijvers over farmacotherapie.

## CONCLUSIES

Ondanks dat wij onafhankelijke risicofactoren voor geneesmiddelgerelateerde problemen gevonden hebben, blijft het moeilijk de patiënten met het hoogste totaal risico op geneesmiddelgerelateerde problemen te selecteren. Totdat een effectief predictiemodel beschikbaar is, zijn interventies op organisatorisch vlak nodig om farmacotherapie te optimaliseren. Deze maatregelen omvatten verbetering van de elektronische voorschrijfsystemen met beslissingsondersteuning en integratie van apothekers in behandelteams die medicatiereviews uitvoeren, zowel in ziekenhuizen als instellingen voor mensen met een verstandelijke beperking.

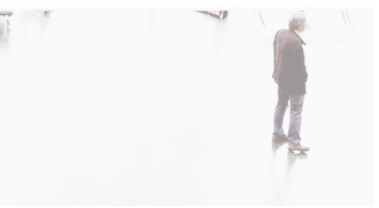
De acceptatie van interventies om geneesmiddelgerelateerde problemen te verbeteren bij individuele patiënten kan worden verbeterd, rekening houdend met de barrières voor acceptatie van artsen. Daarnaast is een beperkte voorschrijfbevoegdheid voor apothekers een interessante mogelijkheid voor het optimaliseren van farmacotherapie.










# Dankwoord

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# About the author

# LIST OF PUBLICATIONS

## Presented in this thesis

R.J. Zaal, M.M.P.M. Jansen, M. Duisenberg-van Essenberg, C.C. Tijssen, J.A. Roukema, P.M.L.A. van den Bemt. Identification of drug-related problems by a clinical pharmacist in addition to computerized alerts. Int J Clin Pharm. 2013;35(5):753-62.

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R.J. Zaal, S. Ebbers, M. Borms, B. de Koning, E. Mombarg, P. Ooms, H. Vollaard, P.M.L.A. van den Bemt, H. M. Evenhuis. Medication review using a Systematic Tool to Reduce Inappropriate Prescribing (STRIP) in adults with an intellectual disability: a pilot study. Submitted.

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K.M. Vermeulen, J.E. van Doormaal, R.J. Zaal, P.G.M. Mol, A.W. Lenderink, F.M. Haaijer-Ruskamp, J.G. Kosterink, P.M.L.A. van den Bemt. Cost-effectiveness of an electronic medication ordering system (CPOE/CDSS) in hospitalized patients. Int J Med Inform. 2014;83(8):572-80.

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# PHD PORTFOLIO

## Summary of PhD training and teaching

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| | PhD period: 1-9-2010 to 1-9-2015 |
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| - Teach the teacher (Erasmus MC Desiderius School) | 2015 |
| - Biomedical English Writing and Communication | 2012 |
| - Research Integrity | 2012 |
| - Pharmacoepidemiology and drug safety (NIHES) | 2012 |
| - Principles of Research in Medicine (NIHES) | 2011 |
| - Introduction to data-analysis (NIHES) | 2011 |
| - Regression analysis (NIHES) | 2011 |
| - Basiscursus Regelgeving Klinisch Onderzoek (Erasmus MC) | 2011 |
| - NIH Course Principles of clinical pharmacology | 2011 |
| **Specific courses (e.g. Research school, Medical Training)** | |
| - Train the trainer and trainees (PUOZ) | 2010 |
| - Medisch Wetenschappelijk Onderzoek met Mensen en Good Clinical Practice | 2010 |
| **Seminars and workshops** | |
| - Vena workshop Networking | 2012 |
| - Methodologie van Patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen | 2011 |
| - Patient Safety in Clinical trials | 2011 |
| - Workshop "Omgaan met groepen" | 2014 |
| - Workshop "Hoorcollege geven" | 2015 |
| **Oral Presentations** | |
| - Physicians' acceptance of pharmacists' interventions in a Dutch university hospital. Prisma Symposium, Amersfoort | 2015 |
| - Evaluation of a systematic tool to reduce inappropriate prescribing (STRIP) in individuals with an intellectual disability: a pilot study. Congress of the European Association of Hospital Pharmacists, Hamburg (Germany) | 2015 |
| - Prescription errors in older individuals with an intellectual disability: prevalence and risk factors. Scientific Meeting NVKF&B, Utrecht | 2012 |
| - Comparison of potential risk factors for medication errors with and without patient harm. Prisma Symposium, Amersfoort | 2011 |

| | Year |
|---|---|
| - Identification of drug-related problems by a clinical pharmacist in addition to computerized physician order entry alerts. Nederlandse Ziekenhuisfarmaciedagen, Nunspeet | 2011 |
| **Poster presentations** | |
| - Physicians' acceptance of pharmacists' interventions in a Dutch university hospital. Scientific Meeting NVKF&B, Utrecht; International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Boston (VS) | 2015 |
| - Evaluation of a Systematic Tool to Reduce Inappropriate Prescribing (STRIP) in individuals with an intellectual disability: a pilot study. Nederlandse Ziekenhuisfarmaciedagen, Rotterdam; International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Boston (VS) | 2014-2015 |
| - Number of biochemical tests as a trigger for adverse drug events. Scientific Meeting NVKF&B, Utrecht; International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Montreal (Canada) | 2013 |
| - Prescription errors in older individuals with an intellectual disability: Prevalence and risk factors. Nederlandse Ziekenhuisfarmaciedagen, Nunspeet | 2012 |
| - Identification of drug-related problems by a clinical pharmacist in addition to computerized physician order entry alerts. International Forum on Quality and Safety in Health Care, Paris (France); Dutch Medicine Days, Lunteren | 2012 |
| - Identification of drug-related problems by a clinical pharmacist in addition to computerized physician order entry alerts. Dutch medicine days, Lunteren | 2011-2012 |
| **(Inter)national conferences** | |
| - International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Boston (VS) | 2015 |
| - Congress of the European Association of Hospital Pharmacists, Hamburg (Germany) | 2015 |
| - PRISMA symposium , Amersfoort | 2011, 2015 |
| - Nederlandse ziekenhuisfarmaciedagen | 2011-2014 |
| - Scientific Meeting NVKF&B, Utrecht | 2012, 2013 |
| - Lareb bijwerkingendag, Utrecht | 2012 |
| - Wetenschappelijke ledenvergadering NVZA-CWZO, Utrecht | 2012, 2010 |
| - International Forum on Quality and Safety in Health Care, Paris (France) | 2012 |
| - Highlights Farmacotherapie, Utrecht | 2012 |
| - Dutch Medicine Days, Lunteren | 2011 |
| **2. Teaching** | |
| Clinical research with medicinal products and good clinical practice | 2011-2015 |
| Practical Course on medication safety for Bachelor's students in medicine | 2012-2015 |
| Pharmacology and pharmacotherapy teaching for Master's students in medicine | 2010-2015 |
| **Supervising Master's theses** | |
| - Annemieke van der Kaaij (Utrecht University) "Prescription errors in older individuals with an intellectual disability" | 2011-2012 |
| - Edwin den Haak (Utrecht University) "Acceptance of pharmacists' interventions" | 2014-2015 |

## CURRICULUM VITAE

Rianne J. Zaal was born on March 30th, 1980 in Veghel and grew up in Made, the Netherlands. After graduating from secondary school at Sint-Oelbert Gymnasium in Oosterhout in 1998, she started her study Pharmacy at the University of Groningen. She obtained her bachelor's degree (cum laude) in 2003 and her Master's degree in 2005.

Subsequently, Rianne started her professional career at the Department of Clinical Pharmacy of the TweeSteden hospital and St. Elisabeth hospital in Tilburg. She participated in a research project on the influence of computerized physician order entry on medication safety, performed in collaboration with the department of hospital and clinical pharmacy of the University Medical Center Groningen. For this project she was honored with the "medication safety award" from the Dutch Association of Hospital Pharmacists (NVZA).

In September 2006, she started her residency training in hospital pharmacy, supervised by A.W. Lenderink and Mrs. M. Duisenberg. During her residency she was a board member of the association of clinical pharmacists in training ("VAZA") in 2008 and 2009.

As of September 2010 she combines a position as hospital pharmacist at the Department of Hospital Pharmacy of Erasmus Medical Center in Rotterdam with a PhD research project, supervised by dr. P.M.L.A. van den Bemt, prof.dr. A.G. Vulto and prof.dr. F.M. Haaijer-Ruskamp, which resulted in this thesis.

Rianne lives together with Jonas and their son Youp in Breda.