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Improving medication safety in surgical patients

Impact of a multifaceted intervention

Jacqueline Maria Bos
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The work presented in this thesis was performed in the Isala Hospital in Zwolle, the Meander Medical Centre in Amersfoort, the Canisius-Wilhelmina Hospital in Nijmegen and the Radboud University Medical Centre in Nijmegen.

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Chapter 1
General introduction
Drugs and harm
Although drugs can cure, they can also cause harm (1-3). The World Health Organization defines an adverse drug reaction (ADR) as “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” (4). It is classified as serious when it is fatal, life-threatening, disabling, incapacitating, or when it results in or prolongs hospitalization (5). An ADR can be caused by drug related factors (drug effects, drug use, synergistic effects between a drug and a disease or between two drugs) and also non-drug related factors (abnormal pharmacokinetics due to genetic factors, age or disease states).

An adverse drug event may result from either appropriate care (non-preventable ADE) or from suboptimal care (preventable ADE). Among all medical adverse events that cause harm, adverse drug events are the most frequent type in patients (6). Medication errors can occur at any stage of the hospital medication process (reconciling, prescribing, dispensing, administering and monitoring), but especially inappropriate prescribing is a frequent cause of ADEs (7). Prescribing errors can have serious consequences and can lead to potentially preventable death, disability, increased length of hospital stay and readmission (3, 8). The drug classes most commonly associated with potentially preventable ADEs are pain medication (non-steroidal anti-inflammatory drugs (NSAIDs) and opioids), (combination of) antitrombotics, certain antibacterial drugs, diuretics, angiotensin-converting enzyme inhibitors, antiepileptic drugs and drugs that are renally excreted (1, 9-14).

Many studies have addressed the nature, occurrence and consequences of medication-related adverse events in the hospital, showing that up to 20-50% of admitted patients experience one or more adverse drug events during their hospital stay. Approximately 50% of ADEs are potentially preventable (1, 9, 11, 15, 16). A high variability in outcome among studies can be explained by the different methods used for measurement, definition and assessment of ADEs (3, 17-22). To measure actual patient harm in terms of death, disability, increased length of hospital stay or readmission, studies with large patient populations are needed. Analysis of these data through assessment by experts is very intensive. Alternative measures, such as quality indicators as process measures, are more efficient in assessing the quality of care, but these measures will only provide an indication of real patient harm.

Patients at risk of adverse drug events
In the last years, a patient population, that is older and more vulnerable, has been growing. These vulnerable patients are often admitted to a hospital because of transient disease, and they frequently need surgical procedures. Surgical patients admitted to the hospital have comorbidities, like heart failure, diabetes or kidney dysfunction, are often treated with multiple high risk drugs and suffer from cognitive and social problems. In case of a surgical procedure, patients are treated with analgesics (NSAIDs and opioids) and frequently antibiotics are given because of the procedure or complications. In addition anticoagulant therapy must be temporarily changed because of the surgical procedure. Diuretics and cardiovascular drugs must be adapted on a day to day basis because of rapid alterations of hydration status due to gastro-intestinal disturbances (bowel obstruction, vomiting, diarrhoea), fever, sweating and lack of intake of fluid and food. Also, these patients are often given radiocontrast for diagnostic procedures. It is known that the complexity of care for these patients contributes to the problem of potentially preventable adverse drug reactions in the hospital. Several studies tried to identify (surgical) patients at risk for adverse drug events and hospital prescribing errors, and different potential risk factors to select high-risk patients have been described (22-26). Organizational factors, such as ward of admission, pharmacy services or staffing, patient related factors such as comorbidity, age, or length of stay and drug related factors have been related to medication errors and adverse drug events. However, results are still inconclusive and it seems even more difficult to translate these findings to a risk prediction model for adverse drug events, that can be automated and made applicable in clinical practice (27-30). Such a model could help to focus safety interventions on high risk patients.

Improvement by education
Pharmacotherapy in high-risk patients in the hospital is very complicated. Prescribing errors defined as ‘irrational, inappropriate and ineffective prescribing, underprescribing and overprescribing’ caused by a lack of clinical pharmacological knowledge might particularly be amenable to a clinical pharmacological educational intervention. It is well known that, in the hospital, the majority of drugs are prescribed by junior medical residents, who are relatively inexperienced and do not feel adequately prepared to do so (31-33). Especially at surgical wards, these junior doctors are supervised by surgeons who often have no specific expertise with respect to complicated pharmacotherapy. The logical strategy to reduce prescribing errors in hospitals by educating the prescriber has been shown to reduce prescribing errors, but this effect is not sustained over time (34). Moreover, it is unclear if education programmes actually reduce patient harm. The development of a more targeted educational programme that covers pharmacotherapy associated with adverse drug events caused by prescribing errors and addresses national and local pharmacotherapeutic guidelines seems useful. This programme should be followed by continuous audit and feedback of the prescriber to boost the effect of education and assures sustainability of knowledge and prescribing behaviour over time.

Support by information technology
Computerized physician order entry (CPOE) with an integrated clinical decision support system (CDSS) supports both the physician and the hospital pharmacist in clinical decision making. It has been shown to reduce medication errors and even ADEs (35). The CPOE-CDSS system currently used in Dutch hospitals, connects to a national database known as ‘G-standard’ and generates a vast amount of alerts of drug-drug interactions, duplicate medication and dosing advices. The most prevalent alerts generated in hospitals concern combinations of NSAIDs, cardiovascular medication and anticoagulants.
However, these alerts are only relevant in a minority of cases and often the physician is unnecessarily warned (36). The aspecificity of the vast amount of alerts generated by the electronic ordering system has led to the situation that some of the more relevant alerts are neglected.

Van der Sijs et al. showed that if the burden of alerts is too high, alert fatigue may cause overriding both important and unimportant alerts, in a manner that compromises the desired safety effect of integrating decision support into computerized physician order entry systems (37, 38).

More advanced clinical decision support systems find their way into daily practice of hospitals. Most Dutch hospitals have implemented ‘clinical rules’ to improve the specificity of the alerts. These clinical rules (advanced CDSS) combine clinical data of the patient (like laboratory results) with the medication to assess whether for instance dose adjustments should be made in case of renal insufficiency (39, 40). The efficiency of alerts has been reported to increase when augmented with an advanced CDSS (41, 42). However, specificity of these clinical rules is still limited and not suitable yet to be integrated into the prescribing workflow of the physician, because not all data needed are digitalised and available and pharmacotherapy is often too complicated to be covered by a set of clinical rules (43).

**Medication review in high risk patients**

Medication review by clinical pharmacists or clinical pharmacologists is deployed to improve prescribing quality in hospital patients. Hereby a systematic assessment of the medication of the patient is performed in combination with assessment of the clinical data of the patient with feedback to their physician or to the patient. It capitalizes on the model of structured interdisciplinary teamwork in a well organised clinical environment in the hospital.

Different methods, such as the Screening Tool of Older Persons’ Prescriptions (STOPP), Screening Tool to Alert doctors to Right Treatment (START) (44, 45) and The Updated Beers Criteria for Potentially Inappropriate Medication Use in older adults (46), although not specifically developed for use in the hospital, can be used by the physician and the hospital pharmacist to perform medication reviews and to design interventions to prevent adverse drug events in hospitalized patients (47).

It is clear from literature that when pharmacists play a proactive role in performing medication reviews, pharmacotherapy for older patients improves (48-50). However, the evidence of the impact of this approach on clinical outcomes such as lowering the incidence rates of adverse drug events or cost effectiveness of care is scarce (51-53).

Moreover, performing medication reviews is time consuming. There is a need for trials in hospitals, to determine the effectiveness and possibilities of medication review in the optimization of pharmacotherapy in hospital patients, in combination with other interventions as education of the prescriber and further development of more advanced clinical decision support systems (54, 55).

### Implementation of guidelines

Clinical practice guidelines with evidence-based recommendations for physicians have been developed to assist doctors and to improve clinician prescribing in hospitalized patients. In routine daily practice however, it appears to be difficult to implement key recommendations and guidelines seem to have a limited ability to change physician prescribing behaviour. The adherence to guidelines by prescribers is inconsistent, despite their potential to improve the quality of health care and patient outcomes (56). Different determinants have been described that prevent or enable guideline adherence (57, 58). When individual health professional factors, such as knowledge, skills and awareness, guideline factors, such as the quality of evidence, local consensus and accessibility of the guideline and other possible barriers are taken into account when developing strategies to improve guideline adherence, the quality of the treatment of hospitalized patients improves (59, 60).

### Organization of care

In recent years, hospital care is characterized by increasing demands for efficiency in health care. 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 7000 deaths annually in the United States at that time (61). 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 Euro per event (1). On the basis of the available literature, an estimate of the proportion of clinically relevant, potentially preventable, drug-related problems due to prescribing errors among patients in the hospital is 0.7%.

Taking into account that in Dutch hospitals per year 680000 patients are admitted on a ward for either surgery (437000 per year) or orthopaedic surgery (251000 per year), this could implicate an incidence of potentially preventable adverse drug events in only surgical patients of 4800 per year. Implementation of strategies to prevent adverse drug events, that lead to death, disability, increased length of hospital stay or readmission is therefore worth the effort of clinical pharmacists and prescribing physicians.

It is important that interventions, that are designed to prevent prescribing errors are cost-effective. Time spent by the hospital pharmacist and the physician on education, implementation of guidelines, optimal use of CPOE-CDSS or performing medication reviews will also incur costs. Through a change of focus to high-risk patients and less focus on low risk patients, these interventions could be more efficient. Less intensive pharmacovigilance in low risk patients can be made possible by optimal use of CPOE/CDSS and for instance automatically settle alerts and clinical rules which are known to be without harm for low risk patients, without intervention by the physician or hospital pharmacist.

Because of a growing need for cost-effective care and a local shortage of medical doctors, as well as concerns about the continuity and safety of clinical processes, another development is that medical ward care is increasingly reallocated to physician assistants (62-64). A physician assistant is a non-physician health care professional licenced to
practice medicine in defined domains, with variable degrees of professional autonomy (65). Since January 2013, PAs are authorized to indicate and perform predefined medical procedures and prescribe medication without supervision. Often, PAs who are employed for medical ward care work in a system of collaborative care that contains PAs, medical doctors (MDs) and hospitalists, comprising a patient medical care team. Although some studies suggest that this reallocation of tasks provides quality and efficiency similar to that of traditional house staff services (66-69), studies on the quality of prescribing, occurrence of prescribing errors or guideline adherence are lacking.

Outline and objective of this thesis

In the Canisius-Wilhelmina hospital we started a multifaceted approach, combining different safety interventions, to address the problem of prescribing errors leading to adverse drug events. An educational programme covering pain management, antithrombotics, fluid and electrolyte management, prescribing in the case of renal insufficiency, application of radiocontrast agents and surgical antibiotic prophylaxis was developed. National and local hospital guidelines related to these subjects were included. Nowadays, this programme is mandatory for all new prescribers in the Canisius-Wilhelmina hospital. In addition, medication reviews are performed by hospital pharmacists and clinical pharmacologists in high-risk patients, that are identified by a computerized screening method. This screening method is based on literature on prescribing errors and targets patients at risk for potentially preventable, drug-related problems. The reviews are performed weekly and discussed with the prescriber (medical doctor or physician assistant) on the ward in so called medication safety consultations (MSC). We assumed that these MSCs would sustain the effect of education on pharmacotherapeutic topics, would promote the accessibility and adherence to guidelines, and could lead to reduction of adverse drug events, less death, disability and readmission, and reduced length of hospital stay. Introducing clinical rules and achieving local agreement on how to assess alerts in CPOE/CDSS in “low risk patients” allows us to focus more on patients at risk for potentially preventable drug related events in our hospital.

Hospital pharmacists and physicians from the surgical wards of the Isala Hospital and the Meander Medical Centre were willing to adopt this multifaceted approach and to cooperate in the P-REVIEW study (Pharmacist-led Risk patients medication Evaluation to Initiate Event reduction on surgical Wards).

General introduction

The main objective of this thesis is to assess the effect of education and support of prescribing physicians at surgical wards on clinically relevant drug-related complications in hospitalised surgical patients, on guideline adherence and costs.

This thesis contains eight chapters. In Chapter 1 the general introduction, the main objective and the outline of this thesis are described.

In Chapter 2 we present an overview of research on the education of prescribers, that reports outcomes on (potential) patient harm. We designed the P-REVIEW study to determine whether a multifaceted intervention of educating the prescriber combined with medication review of high-risk patients and pharmaceutical visits to the ward by the hospital pharmacist could lead to a reduction in clinically relevant drug-related complications among surgical patients. We used a CDSS-based screening method to target patients at risk for potentially preventable, drug-related problems. We also studied the costs that were associated with time spent on study-related activities in Chapter 3.

In Chapter 4 we determined if the approach of the P-REVIEW study combining education of the prescriber with audit and feedback by the hospital pharmacist reduces the non-adherence of prescribers to pharmacotherapeutic guidelines.

In Chapter 5 we used the results of the P-REVIEW study to develop an automated risk prediction model in order to be able to predict which patients are at risk to experience adverse drug events at surgical wards in the hospital.

Chapter 6 describes the effects of substitution of hospital ward care from medical doctors to physician assistants on quality of prescribing of medication.

In the summarizing discussion, Chapter 7, the main results are summarized and discussed in a broader context. Implications for clinical practice and recommendations for future research are provided.

In Chapter 8 the English and Dutch summary are provided.
General introduction


5. EU directive 75/319/EEC. 1975.


Chapter 2

The effect of prescriber education on medication related patient harm in the hospital: a systematic review

Jacqueline Bos
Patricia van den Bemt
Peter De Smet
Kees Kramers

British Journal of Clinical Pharmacology 2017;83:953-61
Abstract

Aims
Educating prescribers is a strategy to reduce prescription errors in hospitals. The present systematic review gives an overview of original research papers on the education of prescribers and reporting outcomes on (potential) patient harm.

Methods
A search of the databases Embase and Medline, using the Ovid interface, was performed. Research on the effect of physician education in order to prevent medication-related problems in inpatients, and on reporting original data and outcomes on prescribing errors and/or (potential) patient harm, was included. The assessment of methodological quality and risk of bias was performed using the Methodological Index for Non-Randomized studies (MINORS) checklist and the suggested risk of bias criteria for Effective Practice and Organization of Care (EPOC) reviews.

Results
Eight studies investigated an intervention on education alone and in seven studies education was the main part of a multifaceted intervention. All studies were small and had short follow up periods. The educational programmes varied and were given to physicians of different specialties and levels of experience. Most studies reported intermediate process parameters as the outcome. The risk of performance and reporting bias were high.

Conclusion
All included studies suffered from poor methodology. The majority, especially studies in which education was part of a multifaceted intervention, reported effectiveness on intermediate outcome markers as prescription errors and potential adverse drug events. However, we found no firm evidence that educating prescribers in the hospital leads to a decreased patient harm. Further work is needed to develop educational programmes, accompanied by more high-quality research with outcomes on the improvement of patient care.

Introduction

Although drugs can cure, they can also cause harm. This holds especially true inside the hospital. Vulnerable patients are often admitted because of a transient disease, and this category of patients that frequently needs surgical procedures. In these patients, prescribing errors can easily have serious consequences. Several papers have addressed adverse drug reactions in the hospital, showing that up to 20% of admitted patients experience adverse drug reactions during hospital stay (1). Risk factors for preventable adverse drug events (ADEs; defined as an injury resulting from the administration of a drug with a causal link to a drug effect) are patient age, time since starting new drug, total number of prescription drugs and type of hospital ward. The drug classes most commonly associated with potentially preventable ADEs are antiplatelet drugs, anticoagulants, diuretics (loop and thiazide diuretics), angiotensin-converting enzyme inhibitors, opioids, antibiotics and antiepileptic drugs (3,4). Many potentially preventable drug reactions are a consequence of inappropriate prescribing by hospital physicians (5).

Many barriers limit the prescribing process, such as information and communications technology (ICT) shortcomings, high workload, increasingly complex polypharmacy and patient factors, lack of standardization and frequent rotations of inexperienced physicians on the ward (6). It is necessary to understand the causes that contribute to prescribing errors, in order to be able to address these factors.

Various strategies, such as the introduction of computerized physician order entry (CPOE), pharmacist involvement, the introduction of protocols, guidelines, education programmes and support systems for clinical decision making (SSCD) have been studied to improve clinician prescribing in hospitalized patients (7-9).

Errors - for example, due to incomplete prescriptions or prescriptions that do not satisfy medication order checklists - can probably best be solved by CPOE with decision support or other strategies, although a combination with a form of education may be useful. Prescribing errors defined as ‘irrational, inappropriate and ineffective prescribing, underprescribing and overprescribing’ caused by a lack of clinical pharmacological knowledge might particularly be amenable to a clinical pharmacological educational intervention.

Therefore, a logical strategy to reduce prescribing errors in hospitals is to educate prescribers. It is well known that, in the hospital, the majority of drugs are prescribed by junior doctors, who do not feel adequately prepared to do so (10). However, it is unclear if education programmes actually reduce patient harm. Various education programmes, with different scopes, have been described. Scientific evaluation of these programs is challenging due to difficulties in blinding and definition of outcome.

Earlier reviews published in this area describe education as one of several possible interventions to improve prescribing quality, examples of others including introduction of CPOE and pharmacist involvement in prescribing. In addition, many of the education programmes in the hospital target nurses, or even the patient, rather than the prescribing physician (7-9).

Other reviews that have reported more specifically on educational interventions have targeted medical students or general practitioners (GPs). Almost every included study has
reported on intermediate endpoints, such as an increase in knowledge or measures of self-assessment instead of improvement of patient care (11-13). Increase in knowledge in these studies has mainly been measured by written examinations. Practical assessments have been based primarily on written patient scenarios, with a limited number of disease topics (11). Although simulation-based education has been shown to improve learning outcomes, the contribution to clinical outcomes remains unclear (14). Moreover, a recent study showed that self-assessment of prescribing skills is poorly correlated with assessed competence (15).

In the present review, we focus on the existing literature on the education of prescribers in hospitals reporting outcomes of (potential) patient harm. We address the scope and form of the education programmes described in the literature and give an appraisal of the scientific merits of the individual studies.

Methods

Search strategy and study selection
A computer-assisted search of the medical databases Embase and Medline using the Ovid interface (from 1990 to May 2016) was performed with the aid of a clinical librarian. A combined search term was constructed as outlined below. The search aimed at finding articles that reported original research data on the prevention of (potential) patient harm due to an intervention involving the pharmacotherapy education of prescribers in a hospital. The search was constructed combining searches according to the PICO (Population: inpatients, Intervention: hospital prescriber education, Comparison: usual care, Outcome: patient harm) model.

The search was performed using MeSH subject headings, combined with keywords to search in the title/abstract and in keyword heading words. Language was restricted to English, Dutch and German.

To retrieve studies on hospitalized patients, the MeSH terms 'Inpatients'; 'Adolescent, hospitalized'; 'Child, hospitalized'; 'Critical care'; 'Emergency service, hospital'; 'Critical care', 'hospitalization', and 'trauma centers' were used. Keywords to search in the title/abstract and keyword heading words were 'inpatient*'; 'hospital*'; 'emergency*'; 'intensive care', and 'critical care'.

The MeSH terms 'physicians'; 'hospitalists'; 'surgeons'; 'physicians/ed'; 'hospitalists/ed'; 'surgeons/ed'; 'education, professional' or 'education, medical'; 'education, medical, continuing'; 'education, medical, graduate'; 'internship and residency' and 'drug therapy' were used to retrieve articles that studied the pharmacotherapy education of doctors. Keywords to search in the title/abstract and keyword heading words were 'educat*'; 'drug therap*'; 'medicat*' and 'polypharmac*'.

To retrieve articles that reported on patient harm caused by prescribing errors the MeSH terms 'Drug-Related Side Effects and Adverse Reactions' and 'Medication Errors' were used. Keywords to search in the title/abstract and keyword heading words were 'adverse drug event'; 'adverse drug reaction'; 'medication error'; 'medication related problem/event/error' and 'prescribing error'.

Appendix 1 shows the search strategy performed in Ovid.

Two independent reviewers (J.B., C.K.) selected the articles that were retrieved from the search. This selection was performed based on titles and abstracts. In the case of disagreement, the full text of the article was retrieved. Research on the effect of pharmacotherapy education on doctors in hospitals in order to prevent medication-related problems in inpatients, and on reporting original data and outcomes on prescribing errors and/or (potential) patient harm was included. The full text of these studies was retrieved. Each of these selected articles was read fully by two authors (J.B., C.K.), who independently assessed whether the articles met the inclusion criteria. In the case of disagreement, consensus was achieved in a consensus meeting. In addition, the reference lists of the selected articles were checked for potentially relevant literature. Research was excluded if the education of doctors in hospitals was only a small part of the intervention.

Assessment of methodological quality and risk of bias

The Methodological Index for Non-Randomized studies (MINORS) checklist, developed by Slim et al. (16) was used for quality assessment of the included studies. This checklist was developed to determine the methodological quality of nonrandomized studies, and consists of 12 methodological items. Eight items are scored for noncomparative studies and four additional items for comparative studies. The items are scored on a three-point scale: 0 (not reported), 1 (reported, but not adequate) or 2 (reported and adequate) (16). To assess the risk of bias, the suggested risk of bias criteria for Effective Practice and Organization of Care (EPOC) reviews were used. These consist of different items regarding risk of bias for interrupted time series (ITS) studies, controlled before-after studies (CBA) and randomized controlled trials (RCTs) (17).

The assessment of methodological quality and risk of bias was performed by two reviewers (J.B., C.K.). In the case of disagreement, consensus was achieved in a consensus meeting. Because of the high heterogeneity between studies in terms of study designs and outcome measures reported, a meta-analysis was not deemed feasible. We therefore provide a descriptive summary of the available evidence.

Results

Search results

The initial literature search strategy yielded 899 articles. A total of 846 articles were excluded after selection, based on title and abstracts and the full text of the remaining 53 articles were retrieved. Based on the full text, 15 articles fulfilled inclusion criteria. The reasons for exclusion of the other articles by the reviewers were that the education was not aimed at prescribers in the hospital (nine articles), no outcome was reported on prescribing errors or (potential) patient harm (20 articles) and no original research was reported (nine reviews and commentaries).

The study characteristics of the selected articles are listed in Table 1. Eight studies investigated an intervention on education of the prescriber alone, and in seven studies the education of the prescriber was the main part of a multifaceted intervention.
Table 1. Overview of selected studies

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>Setting and country</th>
<th>Follow-up</th>
<th>Sample size</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Outcome (prescribing error)</th>
<th>Outcome (potential ADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajemigbitse et al. 2016 [20]</td>
<td>Controlled prospective pre-post intervention study</td>
<td>Tertiary hospitals, Nigeria</td>
<td>6 months</td>
<td>3889 prescriptions preintervention 4361 prescriptions postintervention</td>
<td>Audit on prescribing/ feedback sessions on prescription errors</td>
<td>Prescribing errors</td>
<td>No change in prescribing error rate overall (5.8% vs. 5.8%; P=0.984)</td>
<td></td>
</tr>
<tr>
<td>Foster et al. 2013 [28]</td>
<td>Pre-post intervention study</td>
<td>Pediatric ED, USA</td>
<td>3 months</td>
<td>1101 pharmacy interventions preintervention 1283 pharmacy interventions postintervention</td>
<td>Education on good prescribing/ ED medication and prescription errors, followed by daily feedback on patient cases and therapy</td>
<td>Number of pharmacy interventions, ADEs</td>
<td>Significant decrease in specific pharmacy interventions (dose adjustments and order clarifications)</td>
<td></td>
</tr>
<tr>
<td>Kozer et al. 2006 [24]</td>
<td>Prospective controlled cohort study</td>
<td>Pediatric emergency care Canada</td>
<td>1 month</td>
<td>899 prescriptions</td>
<td>Education on prescribing medication in the ED</td>
<td>Prescribing errors</td>
<td>No difference in prescribing errors between educated and non-educated residents (12.4% vs. 12.7%, OR 1.07)</td>
<td></td>
</tr>
<tr>
<td>Lacombe et al. 2005 [29]</td>
<td>Prospective pre-post intervention study</td>
<td>University hospital, France</td>
<td>6 months</td>
<td>75 patients preintervention, 52 patients postintervention</td>
<td>Providing guidelines on fluoroquinolone utilization/ education session on prescribing errors</td>
<td>Prescribing errors</td>
<td>Decrease in prescribing errors (60.8% vs. 30.8%; P&lt;0.005)</td>
<td></td>
</tr>
<tr>
<td>Peeters et al. 2009 [26]</td>
<td>Prospective interrupted time series analysis</td>
<td>Internal medicine department, University hospital, USA</td>
<td>7 months</td>
<td>38275 prescriptions preintervention, 35441 during intervention, 39031 prescriptions postintervention</td>
<td>Education on safe prescribing, followed by bi-weekly feedback sessions on prescription errors</td>
<td>Prescribing errors</td>
<td>Decrease in prescribing errors during intervention (23% vs. 15%; P&lt;0.001), post-intervention return to baseline (23%)</td>
<td></td>
</tr>
<tr>
<td>Thomas et al. 2015 [31]</td>
<td>Controlled pre-post intervention study</td>
<td>Acute medical unit, 3 hospitals Australia</td>
<td>&lt; 2 months</td>
<td>278 patients preintervention, 271 patients postintervention</td>
<td>Good prescribing (online education and high-intensity education)</td>
<td>Prescribing errors</td>
<td>Decrease in some specific prescribing error rates, no difference in low- and high-intensity education</td>
<td></td>
</tr>
<tr>
<td>Trivalle et al. 2010 [30]</td>
<td>Randomised prospective study</td>
<td>Geriatric centre, public hospital, France</td>
<td>2 weeks</td>
<td>576 elderly patients</td>
<td>Education on ADEs and relevant pharmacotherapy in elderly</td>
<td>ADEs</td>
<td>Decrease in ADEs in intervention group (22% vs. 36% P=0.004)</td>
<td></td>
</tr>
</tbody>
</table>

**Intervention on education as main part of a multifaceted approach**

<p>| Alagha et al. 2011 [32] | Pre-post intervention study         | Paediatric ICU, Egypt              | 5 months  | 13 patients preintervention, 10 patients postintervention | Use of medication order chart, education on good prescribing and feedback on prescription errors of physicians, provision of dosing assistance | Prescribing errors | Significant reduction in prescribing error rate (35.2% vs. 78.1%; P&lt;0.001) |</p>
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>Setting and country</th>
<th>Follow-up</th>
<th>Sample size</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Outcome (potential) ADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burmester et al. 2011[21]</td>
<td>Pre-post intervention study</td>
<td>Paediatric cardiac ICU, USA</td>
<td>3 years</td>
<td>3648</td>
<td>Implementation of a postcardiac surgery templated physician order, systematic physician education on prescribing errors</td>
<td>Prescribing error, potential ADE</td>
<td>Significant reduction of total prescribing errors (16.8% vs. 4.8%; P&lt;0.001)</td>
</tr>
<tr>
<td>Campino et al. 2009[22]</td>
<td>Pre-post intervention study</td>
<td>Neonatal ICU, Spain</td>
<td>7 months</td>
<td>4182</td>
<td>Education on prescribing errors, several preventive strategies as an update of protocols and standardization of medication process</td>
<td>Prescribing errors</td>
<td>Significant reduction of prescribing error rate (20.7% vs. 3.0%; P &lt; 0.001)</td>
</tr>
<tr>
<td>Gabbutt et al. 2008[23]</td>
<td>Pre-post intervention study</td>
<td>Teaching hospital, surgical and medical departments, USA</td>
<td>2 months</td>
<td>2287</td>
<td>Introduction of grand rounds, interactive education on prescribing errors, promoting safe prescribing behaviors</td>
<td>Prescribing error</td>
<td>Significant decrease in prescribing errors by surgical house staff; an increase by medical house staff</td>
</tr>
<tr>
<td>Gazarian et al. 2012[19]</td>
<td>Prospective interrupted time series analysis</td>
<td>Pediatric hospital, Australia</td>
<td>4 years</td>
<td>359 patients preintervention, 326 patients postintervention (4y)</td>
<td>Guideline development and dissemination, intensive interactive education, data feedback</td>
<td>(Potential) ADE, prescribing error</td>
<td>Decrease in prescribing error (4.1% vs. 2.1%; P&lt;0.05) Decrease in potential ADEs (12.3% vs. 4.6%; P&lt;0.05), no decrease in actual or preventable ADEs</td>
</tr>
<tr>
<td>Martinez-Anton et al. 2012[25]</td>
<td>Pre-post intervention study</td>
<td>Pediatric ICU, Spain</td>
<td>4 months</td>
<td>2228</td>
<td>Standardization of prescription sources, update of protocols, education on good prescribing</td>
<td>Prescribing error</td>
<td>Decrease in prescribing errors (21.7% vs. 34.2%; P&lt;0.001)</td>
</tr>
<tr>
<td>Rajamani et al. 2011[18]</td>
<td>Pre-post intervention study</td>
<td>General ICU, Australia</td>
<td>10 weeks</td>
<td>54 patients pre intervention, 58 patients post intervention</td>
<td>Knowledge Translation quality improvement intervention/ education and feedback on prescribing errors</td>
<td>Prescribing errors</td>
<td>Decrease in different prescribing error rates</td>
</tr>
<tr>
<td>Thomas et al. 2008[27]</td>
<td>Pre-post intervention study</td>
<td>ICU, UK</td>
<td>6 weeks</td>
<td>373</td>
<td>Development of standards for safe prescribing, education on good prescribing and problems on ICU, audit and feedback</td>
<td>Prescribing error</td>
<td>Significant decrease of prescribing errors. (incident rate ratio 0.25) Wide variation in prescribing error between trainees</td>
</tr>
</tbody>
</table>

ADE, adverse drug event; ED, emergency department; ICU, intensive care unit; OR, odds ratio
Descriptive summary

Study design
All included studies were relatively small. Sample sizes varied from 112 evaluated patients by Rajamani et al. (18) to 685 patients by Gazarian et al. (19). Several studies reported the total number of prescriptions (20-27) or the number of pharmacy interventions (28) as the sample size. Only two studies made a prospective calculation of the study size using prescription error rates in literature or the results from a pilot study (25, 29).

Most studies had a prospective before-after intervention design; two studies had a prospective ITS design (16, 23), two studies had a CBA design (20, 24) and one study was randomized for the intervention (30). In only one study, a blinded assessment of the outcome parameter was performed (24).

The follow-up of the studies was relatively short, varying from two weeks to a few months. Consequently, the sustainability of the effect of the intervention was poorly investigated. Only the studies by Peeters et al. (26) and Gazarian et al. (19) looked at sustainability after seven months and four years, respectively.

Scope and form of the educational intervention
In seven studies, the intervention was aimed solely at education of the prescriber in the hospital (20, 24, 26, 28-31), and in eight studies the educational intervention was the main part of a multifaceted strategy. In these studies, education was combined with updates and implementation of guidelines and protocols, the introduction of medication order checklists or the performance of audits on the prescribing process (18, 19, 21-23, 25, 27, 32).

Most of the educational programmes that were studied aimed to improve prescribing skills. The definition of these skills varied from prescribing correctly (prevention of incomplete prescriptions) to safer prescribing behaviour and prevention of ADEs. In only a few studies, the educational programme aimed primarily to increase the specific pharmacotherapeutic knowledge of the physicians (29, 30).

The method of educating the prescriber also varied between the studies. For example, Thomas et al. (27) compared online education with high-intensity education sessions. Educational programs were offered to different physicians in different settings. Seven studies describe education to pediatricians (19, 21, 22, 24, 25, 28, 32). Three studies were performed on general intensive care units (18, 27, 31); the others were performed on surgical, internal or geriatric wards (20, 23, 26, 29, 30). Garbutt et al. (23) focused their intervention on surgical house staff and medical house staff. Finally, Thomas et al. (27) looked at education of trainees.

Outcome
Outcomes on potential patient harm were most frequently investigated on intermediate process parameters, with prescribing errors as the main outcome. One study reported the number of pharmacy-interventions (28). A few studies report potential ADEs as an outcome measure (19, 21, 28). Only the study of Trivalle et al. (30) reported ADEs as the main outcome.

Definitions of prescribing errors and (potential) ADEs differed between studies (2).
Discussion

The present review showed that only a relatively small number of studies have evaluated the effects of educational programs for hospital physicians, and of reporting outcomes on (potential) patient harm.

Most studies suffer from poor methodology; the majority of studies were small and the follow-up of the studies was relatively short. The risk of performance bias and reporting bias were high in all of the selected studies.

In half of the studies, education was the main part of a multifaceted intervention and all of these studies showed efficacy on intermediate outcome markers as prescription errors and potential ADEs; this was the case in only four out of seven studies in which the intervention was education alone. The content of the educational programmes and the way of providing the education varied considerably. Different definitions of prescribing errors and ADEs were used, contributing to a large variation in the percentages found.

This large variation can also be explained by the difference in the study settings and in the prescribers targeted in the intervention.

The restriction of the present review to studies of inpatients, in combination with the restriction to outcome measures on prescribing errors and/or patient harm, resulted in the selection of a limited number of studies. We chose to focus on education in the hospital, especially because of the complex patient categories and the specific care environment.

We consider that the effect of education in other settings - for example, nursing homes or GP practice - will be diverse, and measures to improve medication safety, including education, probably need a different approach.

There might have been publication bias on this subject, although we did not find the number of negative studies targeting education alone (20, 24, 27) to be larger than that of positive studies (26, 28-30). However, it is possible that some initiatives on education in hospital practice do not reach the literature, owing to negative outcomes or methodological challenges.

It has been suggested that prevention of patient harm is likely to require complex, multi-faceted intervention strategies (4). This implies that education alone is not likely to have a large (if any) effect, and that education should be embedded in a broader array of measures aimed at appropriate prescribing. All of the studies in which education was a part of a multifaceted approach reported a positive outcome, whereas only four out of seven studies in which the intervention was education alone were positive. This suggests that future research should be targeted towards the most optimal combination of measures - for instance, combining education with implementation of clinical rules (33) and medication reconciliation.

We found considerable methodological limitations in all of the studies, but it should be noted that evaluating education or a multifaceted strategy including education cannot easily be performed in RCTs. Instead, a CBA/ITS design or a cluster RCT must be used, all of which have their inherent methodological limitations and challenges. However, blinded evaluation of clinical relevant outcomes is important, given the subjectivity of definition of ADEs. In addition, sustainability is an important aspect that should be addressed. In the case of a CBA design or an ITS, a control group without intervention should be included. The outcome of any research regarding this subject should be improvement of patient care, preferably using clinically relevant endpoints.

Although it is plausible that patients will benefit from educating hospital prescribers in pharmacotherapy, the present review showed that further work is needed to develop effective educational interventions and to perform robust evaluations.

The knowledge of how to teach effectively should be combined with optimizing the content of education. At present, there are no data supporting a specific form of education. A recent article of Franchi et al. (34) showed that an e-learning educational program alone failed to improve clinician drug prescription for hospitalized older patients. One of the authors’ suggested explanations for failure was the low level of interactivity of the program. In addition, they suggested that educational programs need a follow up, to enhance learning retention. The authors also indicated that education should...
be combined with different strategies in a multifaceted intervention to obtain a real
improvement in prescription quality (34).
The qualifications or training of teachers that deliver the educational interventions was
rarely addressed in the included studies. This could also have influenced the quality of the
intervention and the outcomes.
The present review suggested that educational sessions should be combined with other
measures to improve medication safety. In regard to the form of education, there are
indications that workplace-based pharmacotherapy education, using complementary
knowledge in interdisciplinary settings is most effective (35). With continuous audit and
feedback on the main pharmacological issues and prevailing guidelines in the workplace
of healthcare professionals, there will be a higher likelihood of a sustained effect.
Moreover, in our opinion, this educational approach should start early in the programmes
of undergraduates. Clinical pharmacological teaching involving students in prescribing in
‘real context’ training programmes, in addition to more classical teaching, has been
described to be of great educational value (36). Furthermore, in our view, the content of
pharmacology education should be related to known risk factors for medication errors in
hospital patients and should focus on the use of high-risk drugs in high-risk patients or
high-risk situations. In addition, education should also cover correct use of the electronic
prescribing system and a clinical decision support system.

Conclusion
Taken together, there is currently no firm evidence that educating prescribers in the
hospital leads to a decrease in patient harm. However, there is also no sound research
showing that education has no effect, and many studies, especially those with the
multifaceted interventions, have shown benefit on intermediate outcome parameters.
Future research should be targeted at development and implementation of educational
programmes, with outcomes on improvement of patient care, which should be
evaluated by high-quality research. In our view, these programmes should be a part of a
multifaceted approach in which education is supported by other measures. It is hoped
that this will result in evidence for measures which can be taken to improve medication
safety in the hospital.

Appendix 1.
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid
MEDLINE(R) <1946 to Present>
Search Strategy:
1. adolescent, hospitalized/ or child, hospitalized/ or inpatients/ or inpatient?.tw. or inpatient?.kf. or
hospital*.tw. or hospital*.kf. or exp critical care/ or hospitalization/ or emergency service, hospital/
 or trauma centers/ or emergenc*.tw. or emergenc*.kf. or ((intensive or critical) adj3 care).tw. or
 (intensive or critical) adj3 care.kf. (1320173)
2. physicians/ or hospitalists/ or surgeons/ or physicians/ed or hospitalists/ed or surgeons/ed or
education, professional/ or education, medical/ or education, medical, continuing/ or education,
 medical, graduate/ or “internship and residency”/ or ed.fs or educat*.tw. (706878)
3. exp Drug Therapy/ or ((drug adj3 therap*) or medicat* or polypharmac*).tw. or ((drug adj3 therap*) or
medicat* or polypharmac*).kf. (1373658)
4. 1 and 2 and 3 (7555)
5. dt.fs. (1855920)
6. 3 or 5 (2637038)
7. 1 and 2 and 6 (9757)
8. “Drug-Related Side Effects and Adverse Reactions”/ or Medication Errors/ or (adverse adj3 drug adj3
(event? or reaction?)).tw. or ((medicat* adj3 error?) or (medicat* related adj3 (problem? or event?
or error))).tw. or (prescribing adj3 error?).tw. or (adverse adj3 drug adj3 (event? or reaction?)).kf. or
 ((medicat* adj3 error?) or (medicat* related adj3 (problem? or event? or error))).tw. or (prescribing
adj3 error?).kf. (496277)
9. 7 and 8 (977)
10. (dutch or english or german).la. (22079904)
11. 9 and 10 (928)
12. limit 11 to yr="1990 -Current" (899)
References


17. EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services. Effective Practice and Organisation of Care (EPOC). Suggested risk of bias criteria for EPOC reviews. 31-12-2015 [online]. Available at http://epoc.cochrane.org/epoc-specific-resources-review-authors (last accessed October 2016).


A multifaceted intervention to reduce drug-related complications in surgical patients

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Patricia van den Bemt
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Abstract

Aim
The P-REVIEW study was a prospective, multicenter, open intervention study, designed to determine whether a multifaceted intervention of educating the prescriber combined with medication review and pharmaceutical visits to the ward by the hospital pharmacist could lead to a reduction of drug-related complications among surgical patients.

Methods
A total of 6780 admissions of 5940 patients to surgical, urological and orthopaedic wards during the usual care period and 6484 admissions of 5711 patients during the intervention period were included. An educational programme covering pain management, antithrombotics, fluid and electrolyte management, prescription in case of renal insufficiency and antibiotics was developed. National and local hospital guidelines were included. Hospital pharmacists performed medication safety consultations, combining medication review of high-risk patients and a visit to the physician on the ward.

Results
A significantly lower proportion of admissions with one or more clinically relevant, potentially preventable, drug-related problems (including death, temporary or sustained disability, increased length of hospital stay or readmission within 30 days) occurred in the intervention period (1.1% [73/6484] compared to the usual care period (1.6% [106/6780]) (P=0.029). The relative risk (RR) was 0.72 (95% CI 0.53-0.97). Several types of drug-related problems occurred less frequently. Costs incurred as result of time spent on study-related activities were not different before and after the intervention.

Conclusions
The P-REVIEW study shows that education and support of the prescribing physician with respect to high-risk patients in surgical departments leads to a significant, clinically relevant benefit for patients without generating additional costs.

Introduction
Problems due to errors in pharmacotherapy are common among hospitalized patients (1-4). Many of these derive from prescribing errors that lead to potentially preventable morbidity, mortality and costs. The majority are caused by pain medication (non-steroidal anti-inflammatory drugs (NSAIDs) and opioids), (combination of) antithrombotics, antibacterial drugs, cardiovascular drugs, and drugs that are renally excreted (1-3, 5, 6). Especially patients on surgical wards are at risk, due to the need for pain medication and antibiotics, frequent adjustments of antithrombotic regimens and blood and fluid loss (7).

In the case of elderly surgical patients, multiple co-morbidities requiring multiple drugs add even more to the potential drug-related problems (8). The care for these patients is often provided by junior physicians. These junior doctors do not consider themselves sufficiently trained to prescribe (9-11) and they are often supervised by surgeons who have no specific expertise with respect to complex pharmacotherapy. Guidelines have been developed to assist doctors and improve care, but implementation of these guidelines is challenging and adherence is limited, possibly because of frequent rotations of inexperienced physicians on these wards (12, 13).

Several approaches may be considered to minimize prescription errors. It was shown that implementation of a comprehensive checklist, including medication-related items, can reduce surgical complications and mortality (14). In addition, computerised physician order entry (CPOE) in combination with a clinical decision support system can support both the physician and the hospital pharmacist. However, some prescription errors may still be missed (15, 16), while at the same time alert fatigue may arise as the result of irrelevant alerts, increasing the likelihood that important alerts go unnoticed (17, 18). The inexperienced physician on the ward lacks adequate knowledge to interpret the alerts. In most hospitals, overridden alerts are checked by hospital pharmacists. However, for a comprehensive judgement of the medication of the patient by the hospital pharmacist, detailed knowledge about the clinical situation is needed. This has led to more active involvement of hospital pharmacists on clinical wards. This approach, however, is time consuming. Despite research, that demonstrates the benefits of different clinical pharmacy services (19-21), there is only scarce evidence of benefit on clinically relevant outcome measures for patients on general (non-ICU) wards (22-24).

Another strategy to reduce prescribing errors aims at educating the prescriber. Although this has been shown to reduce prescribing errors, the effect is not sustained over time (25). An educational programme could be made more sustainable by combining it with pharmaceutical care visits by the hospital pharmacist to the ward. The educational programme teaches the pharmacological aspects of using high-risk drugs in high-risk patients. The goal of the visits by the hospital pharmacist is to boost the effects of education and to suggest interventions based on a medication review of the patient. By discussing prescribing errors these medication reviews will also have an educational effect. To reduce the workload of the hospital pharmacist and to improve feasibility of the intervention, patients at risk of drug-related problems, are selected based on medication use and clinical features. Guidelines (e.g. on peri-operative anticoagulation policy) are an important part of the educational programme. The visiting hospital pharmacist actively checks and teaches on guideline adherence.
The P-REVIEW study (Pharmacist-lead Risk patients medication Evaluation to Initiate Event reduction on surgical Wards) was designed to investigate whether such an approach could lead to a reduction of drug-related complications among high-risk surgical patients.

Methods

Study design and setting
The P-REVIEW study was an open intervention study with a before-after design performed in two large general teaching hospitals in the Netherlands (the Isala Hospital in Zwolle, 779 beds and the Meander Medical Centre in Amersfoort, 600 beds). In total, 12 hospital pharmacists participated in the study. The institutional review boards of the Isala Hospital and the Meander Medical Centre stated that the study was exempt from ethical approval. Patient data were collected and stored in accordance with prevailing privacy regulations.

Study population
All patients who were admitted to the surgical, urological and orthopaedic wards of the two hospitals during a usual care period (1 June 2011-1 December 2011) and an intervention period (1 March 2012 - 1 September 2012) were included in the study. Both periods were of six months duration, with a three-month period in between, during which the intervention was introduced. Patients were followed up until discharge. Patients could be included more than once, in case of readmission. Day care patients were excluded.

Usual care period
During the usual care period, the normal procedures of medication surveillance and communication between hospital pharmacists and physicians were maintained. A computerized physician order entry (CPOE) system with clinical decision support (CDS) was applied in both hospitals. There was no orthogeriatric service at the time of the study. Briefly, hospital pharmacists checked medication of all patients on a daily basis with the aid of computer-generated alerts based on a national database (‘G-standard’; www.z-index.nl). Hospital pharmacists could warn the physician by telephone or send a fact-sheet to the ward. In both hospitals, pharmacists were supported by a set of computerized ‘clinical rules’ to screen for specific prescription errors. These clinical rules combine clinical patient data (like renal function and electrolyte abnormalities) with the medication to judge, for example, whether dose adjustments should be made in case of renal insufficiency or if gastric protection should be added to an NSAID (26).

Intervention period
During the intervention, a combination of an educational programme and medication counselling for prescribers dealing with high-risk patients on the wards took place, in addition to the procedures described above.

An educational programme covering pain management, antithrombotics, fluid and electrolyte management, prescription in the case of renal insufficiency, application of radiographic contrast agents and surgical antibiotic prophylaxis was developed.

The programme consisted of two parts of approximately 2 hours each. All prescribers on the participating wards attended the course.

Hospital pharmacists were trained to perform medication safety consultations (MSC), combining a medication review and a visit to the ward. A computerised screening method identified high-risk patients. The screening method was based on recent literature on prescription errors and targeted patients at risk for potentially preventable, drug-related problems (1, 27) (Appendix 1). Hospital pharmacists performed the medication review by using a checklist, in order to establish uniformity (Appendix 2). The review was performed weekly and discussed with the prescriber on the ward.

Study endpoints
The primary outcome of this study was the proportion of patients with one or more potentially preventable, clinically relevant, drug-related problems. Clinically relevant problems included death, temporary or sustained disability, increased length of hospital stay or readmission within 30 days. Secondary endpoints were characterization of drug-related problems and costs that were incurred by the hospital as a result of running the programme.

Data collection
Collected data included patient characteristics, laboratory and medication data, as well as admission mutations, medical correspondence and medical interventions. Data regarding radiology, microbiology, blood transfusion and information about medical incidents were also collected.

A semi-automatic trigger instrument using electronic patient records was used to identify possible drug-related problems based on these data (Appendix 3). It consisted of a comprehensive set of phenomena such as (change in) laboratory results, medication use, clinical interventions (e.g. gastroscopy), radiology examinations, consultations of other specialists, transfer to the intensive care unit, readmission within 30 days and death (1, 28-31). Assessment of triggers and filling out of the case report was performed at least two weeks after discharge or death of the patient to avoid influencing daily practice. The major part of the data collection and the identification of possible cases with a clinically relevant, drug-related problem based on the trigger list was performed automatically, using a validated multisource Microsoft Access database (Microsoft version 2003). In addition, some of the data were collected manually and edited by a trained research assistant in the hospital using a predefined protocol (Appendix 3).

Recommendations on pharmacotherapy, based on the MSC, performed by the hospital pharmacist during the invention period, were documented in the database. On the fifth month of both periods, pharmacy assistants and hospital pharmacists registered the time they spent on activities such as checking prescribed medication and interventions performed. In the intervention period they also registered time spent on activities such as medication review of high-risk patients and medication safety consultation on the ward. They also made an estimate of the time spent by the prescribing physician to follow up the advice. Time spent on the educational programme by hospital
A multifaceted intervention to reduce drug-related complications in surgical patients

The mean total costs were €6.04 (95% CI: 5.82-6.26) per admission in the usual care period. The costs per admission were significantly lower for hospital pharmacists because they performed MSC and ward visits. The costs were also registered.

Costs were calculated by multiplying the time spent on the study-related activities by salary expenditures of health-care providers, obtained from the collective labour agreement of Dutch hospitals (www.nvz-ziekenhuizen.nl).

Baseline characteristics were presented as means and standard deviation or percentages for continuous or dichotomous outcomes, respectively.

Sample size and data analysis

On the basis of the available literature, we estimated that the proportion of clinically relevant, potentially preventable, drug-related problems among surgical patients would be 0.7% (36).

Our study was powered to detect a reduction of this proportion by at least 50%. A two-group, Chi square test with a 0.05 one-sided significance level will have 80% power to detect such difference when the sample size per group is 5300.

Baseline characteristics were presented as means and standard deviation or percentages for continuous or dichotomous outcomes, respectively.

Differences between groups were tested on statistically significant difference with either an independent t-test or a chi-square test depending on type of data.

The difference in proportion of clinically relevant drug-related complications was expressed in relative risk with 95% confidence interval. In addition, the average number of high-risk patients needed to review in order to prevent one clinically relevant drug-related complication was calculated (1/ARR). As a secondary analysis, the relative risk (RR) of clinically relevant drug-related complications between the two periods was corrected for confounders using binominal logistic regression. Age, gender, department where the admission took place and whether or not the admission was planned were considered as confounders and included in the regression analysis as fixed factors.

Costs were compared between the two periods with a student’s t-test. Statistical analyses were performed using SPSS Statistics version 21.

Results

In the usual care period of the study, 6780 admissions (5940 patients) and in the intervention period 6484 admissions (5711 patients) were included. Table 1 details the characteristics of these admissions.

A significantly lower proportion of admissions with one or more clinically relevant, potentially preventable, drug-related problems occurred in the intervention period (1.1% (73/6484) compared to the usual care period of the study (1.6% (106/6780)) (P=0.029). The relative risk (RR) was 0.72 (95% CI: 0.53-0.97).

After correction for potential confounders (age, gender, department, planned admission) the adjusted RR was 0.74 (95% CI: 0.54-1.00) (Table 1).

When the included patients were divided into the predefined risk classes the primary end point changed from 3.7% (89/2392) to 2.8% (61/2126) in high risk patients; RR 0.77 (0.55-1.06); and from 0.4% (17/4388) to 0.3 % (12/4358) in low risk patients; RR 0.71 (0.34-1.49). The average number of high-risk patients that needed to be reviewed in order to prevent one clinically relevant drug-related problem was 111 (100/0.9).

Table 2 shows a comparison of intervention-related characteristics. There was no difference in the number of medications the first day after admission. However, there was a (small) decrease in the percentage of admitted patients using specific medication groups. In some groups (heparin/LMWH, diuretics, beta blockers, opioids) this reduction was statistically significant.

In addition, length of hospital stay and the number of patients with renal insufficiency was decreased after the intervention.

Table 3 describes the characteristics of the patients with an event. The patients who had an event were older and used more drugs at the first day after admission. The mean length of hospital stay of these patients was slightly shorter after the intervention than in the usual care period. The mean time until the occurrence of the event showed no difference between the two periods.

Table 4 describes the types of events in patients with a drug-related problem. Several types of events occurred less frequently during the intervention period, especially haemorrhage, thrombosis and central nervous systems events (mainly delirium).

Table 5 shows the costs of study-related activities during the usual care period and the intervention period of the study. During the intervention, the costs per admission were higher for hospital pharmacists because they performed MSC and ward visits. The costs of pharmacy assistants, however, were lower. Costs of the training of pharmacists and prescribers were assessed and expressed as extra costs per admission. Taken together, mean total costs were €6.04 (95% CI: 5.82-6.26) per admission in the usual care period. These were not statistically significant different from €6.18 (95% CI: 6.06-6.30) per admission in the intervention period.
A multifaceted intervention to reduce drug-related complications in surgical patients

Table 1. Characteristics of admissions

<table>
<thead>
<tr>
<th></th>
<th>Usual care period</th>
<th>Intervention period</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of admissions</td>
<td>6780</td>
<td>6484</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>5940</td>
<td>5711</td>
<td></td>
</tr>
<tr>
<td>Mean age of patients in years ± SD</td>
<td>63.3 ± 17.6</td>
<td>62.2 ± 17.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender of patients, n (%) female</td>
<td>3380 (49.9 %)</td>
<td>3238 (49.9%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Department of admission</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- General surgery, n (%)</td>
<td>3947 (58.2%)</td>
<td>3727 (57.5%)</td>
<td></td>
</tr>
<tr>
<td>- Orthopaedic surgery, n (%)</td>
<td>1595 (23.5%)</td>
<td>1455 (22.4%)</td>
<td></td>
</tr>
<tr>
<td>- Urology, n (%)</td>
<td>1238 (18.3%)</td>
<td>1302 (20.1%)</td>
<td></td>
</tr>
<tr>
<td>Planned admission, n (%)</td>
<td>2306 (35.2%)</td>
<td>2217 (34.2%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table 2. Comparison of intervention-related characteristics

<table>
<thead>
<tr>
<th></th>
<th>Usual care period (n = 6780)</th>
<th>Intervention period (n = 6484)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no. of medications the first day after admission, ± SD</td>
<td>6.65 ± 5.54</td>
<td>6.57 ± 5.65</td>
<td>0.397</td>
</tr>
<tr>
<td>Medication the first day after admission, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hypoglycemics</td>
<td>846 (12.5%)</td>
<td>717 (11.1%)</td>
<td>0.011</td>
</tr>
<tr>
<td>- Vitamin K antagonists</td>
<td>598 (8.8%)</td>
<td>531 (8.2%)</td>
<td>0.193</td>
</tr>
<tr>
<td>- Heparin/LMWH</td>
<td>4298 (63.4%)</td>
<td>3893 (60.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Thrombocyte aggregation inhibitors</td>
<td>1245 (18.4%)</td>
<td>1223 (18.9%)</td>
<td>0.460</td>
</tr>
<tr>
<td>- Diuretics</td>
<td>1578 (23.3%)</td>
<td>1342 (20.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Beta blockers</td>
<td>1632 (24.1%)</td>
<td>1372 (21.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Calcium channel blockers</td>
<td>641 (9.5%)</td>
<td>687 (10.6%)</td>
<td>0.029</td>
</tr>
<tr>
<td>- RAS inhibitors</td>
<td>1654 (24.6%)</td>
<td>1453 (22.4%)</td>
<td>0.007</td>
</tr>
<tr>
<td>- NSAIDs</td>
<td>2381 (35.1%)</td>
<td>2201 (33.9%)</td>
<td>0.156</td>
</tr>
<tr>
<td>- Opioids</td>
<td>2733 (40.3%)</td>
<td>2398 (37.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Antipsychotics</td>
<td>419 (6.2%)</td>
<td>346 (5.3%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Mean length of stay, days ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- General surgery</td>
<td>6.9 ± 8.7</td>
<td>5.7 ± 6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Orthopaedic surgery</td>
<td>6.7 ± 7.2</td>
<td>6.0 ± 5.6</td>
<td>0.005</td>
</tr>
<tr>
<td>- Urology</td>
<td>4.1 ± 4.3</td>
<td>3.7 ± 3.4</td>
<td>0.027</td>
</tr>
</tbody>
</table>

MDRO cGFR of patients (mL/min/1.73 m²), n (%) | (n = 4637°) | (n = 4259°) | 0.006 |
| - <10                     | 34 (0.7%)                  | 30 (0.7%)                   |         |
| - 10-30                   | 146 (3.1%)                 | 150 (3.5%)                   |         |
| - 30-60                   | 972 (21.0%)                | 835 (19.6%)                  |         |
| - >60                     | 3485 (75.2%)               | 3243 (76.2%)                 |         |

a Number of admissions during which a MDRD of the patient was measured

LMWH = low molecular weight heparin; NSAIDs = non-steroidal anti-inflammatory drugs; RAS = renin angiotensin system

Table 3. Characteristics of patients with an event

<table>
<thead>
<tr>
<th></th>
<th>Usual care period</th>
<th>Intervention period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of patients in years ± SD</td>
<td>78.6 ± 8.7</td>
<td>74.8 ± 13.9</td>
</tr>
<tr>
<td>Female patients, n (%)</td>
<td>51 (48.1%)</td>
<td>34 (46.6%)</td>
</tr>
<tr>
<td>Department</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- General surgery, n (%)</td>
<td>74 (69.8%)</td>
<td>43 (58.9%)</td>
</tr>
<tr>
<td>- Orthopaedic surgery, n (%)</td>
<td>28 (26.4%)</td>
<td>22 (30.1%)</td>
</tr>
<tr>
<td>- Urology, n (%)</td>
<td>4 (3.8%)</td>
<td>9 (11.0%)</td>
</tr>
<tr>
<td>Mean no. of medications the first day after admission, ± SD</td>
<td>11.1 ± 4.9</td>
<td>12.4 ± 5.1</td>
</tr>
<tr>
<td>Mean length of stay, days ± SD</td>
<td>14.2 ± 10.4</td>
<td>13.1 ± 9.7</td>
</tr>
<tr>
<td>Mean duration until occurrence of event (including events, leading to readmission), days ± SEM</td>
<td>6.7 ± 0.7</td>
<td>6.8 ± 0.8</td>
</tr>
</tbody>
</table>

Table 4. Clinically relevant, potentially preventable, drug-related problems due to prescription errors: type of events

<table>
<thead>
<tr>
<th></th>
<th>Usual care period 106a (1.6%)</th>
<th>Intervention period 73b (1.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage (NSAID, antithrombotic therapy)</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Arterial or venous thrombosis (antithrombotic therapy)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Renal insufficiency, hydration or electrolyte related event (diuretics, NSAID, RAAS inhibitors)</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Drug intoxication in renal insufficiency (unadjusted therapy)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Central nervous systems events mainly delirium (tramadol, anticholinergic therapy)</td>
<td>48</td>
<td>20</td>
</tr>
<tr>
<td>Faecal impaction (opiates)</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Hypoventilation (opiates)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unclassifiablea</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

a These drug-related problems occurred in 102 patients in the control period and 69 patients in the intervention period.
b Variable drug-related problems, for instance Addison crisis because of omission of corticosteroids; prescribing salbutamol to a patient, with a known allergy to salbutamol; lithium intoxication because of drug-drug interaction; pulmonary edema, provoked by naproxen.
A multifaceted intervention to reduce drug-related complications in surgical patients

The P-REVIEW study has several strengths. The intervention combines two strategies which have been employed separately in the past: structured medication reviews followed by visits to the ward by the hospital pharmacist and education of prescribers. Both interventions have been found to be effective in reducing drug-related problems, but the effect on clinically relevant endpoints was still unknown. Education of prescribers has been found to have only a transient effect on the frequency of prescription errors (25). In our study we aimed to boost this effect by the weekly visits of the hospital pharmacist as a form of workplace-based pharmacotherapy education.

Furthermore we used risk stratification to make the efforts of the hospital pharmacist more efficient. As one of the purposes of the weekly medication review and the visits to the ward was education of prescribers, we reasoned that we did not need to address all possible prescription errors. We showed that low-risk patients (without medication review) may also benefit from the effect of the intervention.

As the primary outcome we studied clinically relevant patient outcome measures (death, temporary or permanent disability, increased hospital stay or readmission) in a very large patient cohort. Prescription errors, leading to these clinically relevant drug-related problems, were identified in a broad perspective, including possible adverse drug reactions, drug interactions, guideline non-adherence and omission of medication.

The intervention was performed by healthcare providers already active in the hospital, so implementation was relatively straightforward. The study was performed in two large teaching hospitals that are representative for the majority of hospitals in the Netherlands. Besides these strengths, the study also has a number of limitations. The study had a before-after design. Therefore, it is impossible to ascertain whether differences in characteristics, such as the use of certain drugs, are caused by the intervention or should be ascribed to differences between the groups. We considered a randomised controlled design impossible, since both the educational programme and the visit by the pharmacist will contaminate usual care as residents and other healthcare providers learn from this intervention. By blinding all case record forms with respect to the study period before assessment by the experts and by correcting for confounders, the probability of bias was minimized.

Next, the study was performed in two hospitals in the Netherlands possibly limiting the external validity of the study. The role of the hospital pharmacist on the ward can be different in other countries. This study used a trigger instrument to identify clinically relevant, medication-related events, based on different trigger instruments described in the literature. However, this has not been formally validated and therefore some events might have been missed. Nevertheless, as events will have been missed both before and after, this may only limit the power of the study, without biasing the outcome.

The cost analysis shows that this intervention does not lead to extra costs. However, in the analysis only time spent by healthcare workers was taken into account. Possible effects on medication use and laboratory tests were not included, but the costs of the drug-related complications were not calculated either.

Table 5. Mean costs of usual care and of intervention (pharmaceutical care and training of prescribers) per admission

<table>
<thead>
<tr>
<th>Mean costs per admission (€)</th>
<th>Usual care period</th>
<th>Intervention period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy assistants</td>
<td>€ 4.86</td>
<td>€ 2.16</td>
</tr>
<tr>
<td>Hospital pharmacists</td>
<td>€ 1.08</td>
<td>€ 1.90</td>
</tr>
<tr>
<td>Prescribers</td>
<td>€ 0.10</td>
<td>€ 0.15</td>
</tr>
<tr>
<td>Training of prescribers</td>
<td>€</td>
<td>€ 1.97</td>
</tr>
<tr>
<td>Total</td>
<td>€ 6.04 (95% CI: 5.82-6.26)</td>
<td>€ 6.18 (95% CI: 6.06-6.30)</td>
</tr>
</tbody>
</table>

Discussion

The P-REVIEW study shows that a teaching programme for prescribers, combined with performing medication reviews in patients, at risk for drug-related problems, and weekly visits of a hospital pharmacist to the ward significantly reduces clinically relevant, potentially preventable, drug-related problems in patients admitted to surgical wards. The results reveal a significantly lower proportion of admissions with one or more of these problems in the intervention period. Costs incurred by the hospitals did not increase during the intervention period as the result of time spent on education, medication review and ward visits by hospital pharmacists.

P-REVIEW is a study with clinically relevant outcome measures in a very large patient cohort. Different interventions to minimize medication errors such as medication review, medication reconciliation, computerised physician order entry system with clinical decision support, educational programmes and multifaceted approaches have been studied before. These studies were generally insufficiently powered and focused on surrogate endpoints such as prescription errors, medication discrepancies or prevention of potential harm. The studies showed substantial heterogeneity in these outcomes. Some studies indicate that these interventions improve patient management or clinically relevant outcomes (19). However, most studies were methodologically weak, as they used non-blinded designs and lacked robust data collection methods (15, 37-46).

In two smaller studies it was shown that educational programmes reduced prescription errors in the ICU and among hospitalized elderly, although they failed to show an effect on clinically relevant outcomes (45, 47). When education was incorporated in a multifaceted approach, hospital anticoagulation management improved, which led to reduction of venous thromboembolism (VTE) and costs (48). Reduction of VTE was also found after implementation of a computerized clinical decision support system (49). Decision support plus validation by a pharmacist led to more efficient pharmaceutical care on the ICU and reduction of potential prescribing errors on clinical wards in a tertiary referral hospital, but did not show improvement on clinically relevant patient outcomes (50, 51). The SUREPILL study, which evaluated a protocolled, ward-based pharmacy method compared with standard pharmaceutical care in surgical patients, showed no reduction in medication-related harm or changes in clinical outcomes (24).
A multifaceted intervention to reduce drug-related complications in surgical patients

This study shows that introducing a teaching programme for prescribers, combined with performing medication reviews in high-risk patients and weekly visits of a hospital pharmacist to the surgical ward, contributes to patient safety and should be implemented in all hospitals. The implementation of these activities is relatively easy and can be performed by healthcare providers already active in the hospital. The time and effort needed from the hospital pharmacist to perform MSC and ward visits and to train prescribers are compensated by less time consumed by pharmacy assistants probably due to less need for interventional activities. Although on first sight reducing clinical relevant drug related errors from 1.6 to 1.1 % seems not especially impressive, one has to take into account that each year in the Netherlands 4 million hospital admissions take place. This means that thousands of patients would benefit from nationwide implementation of this intervention.

Further investigation should address improvement of the identification of high-risk patients. We intend to perform a post-hoc analysis of the P-REVIEW database to identify more specific predictive factors for patients at risk for clinically relevant preventable medication related adverse events. Being able to more accurately predict which patients are at risk for a drug-related complication during hospital admission would improve the efficiency of interventions. The method used for risk identification could be different between hospital wards of different medical specialties.

In addition, we intend to investigate whether the implementation of education of prescribers and performing medication reviews also has an effect on relevant patient outcomes in non-surgical medical specialties as internal medicine, neurology or psychiatry.

In summary, this large study shows that education and support of the prescribing physician by the hospital pharmacist with respect to high-risk patients in surgical departments leads to a significant clinically relevant benefit for patients. This study also shows this helps reduce clinically relevant medication-related problems without generating additional costs.

Acknowledgements

We would like to express our gratitude to the hospital pharmacists and to the physicians of the surgical, orthopaedic surgical and urological wards of the Meander Medical Centre in Amersfoort and the Isala Hospital in Zwolle.

Appendix 1. Screening method to identify high-risk patients on surgical wards

All patients with renal insufficiency (MDRD < 60ml/min/1.73m2)
or use of high-risk medication or medication combinations:
- Renin angiotensin aldosterone system (RAAS) inhibitor and loop diuretic
- RAAS inhibitor and loop diuretic and non-steroidal anti-inflammatory drug (NSAID)
- (Coumarin or heparin or high-dose low molecular weight heparin (LMWH)) and Adenosine diphosphate (ADP) receptor antagonists (e.g. clopidogrel)
- (Coumarin or heparin or high-dose LMWH) and acetylsalicylic acid
- (Coumarin or heparin or high-dose LMWH) and NSAID
- ADP receptor antagonists and acetylsalicylic acid
- NSAID and (coumarin or serotonin-specific reuptake inhibitor (SSRI) or prednisone or acetylsalicylic acid)
- Use of digoxin, sotalol, lithium, aminoglycosides or methotrexate
Appendix 2. Checklist for performing medication review on surgical wards

The checklist below is not meant to be complete, but is meant to support the hospital pharmacist in performing medication review and to establish uniformity.

<table>
<thead>
<tr>
<th>Clinical consideration</th>
<th>Relevant conditions</th>
<th>Drugs concerned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- What is the MDRD?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Muscle mass abnormal?</td>
<td>e.g. wheel chair, neuromuscular disease, amputation, &gt;2 weeks bedridden</td>
<td>prednisone</td>
</tr>
<tr>
<td>- Dose adjustments necessary for medication with narrow therapeutic indexes that are processed by the kidneys or contraindication?</td>
<td>NSAID, digoxin, zotal, lithium, metformin, therapeutic dose LMWH, nitrofurantoin, aciclovir, amnoglycocico, atenolol, SU derivate etc.</td>
<td></td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hypoatraemia &lt; 135 mmol/l?</td>
<td>(Combination of two of the three of) SSR, thiazide, carbamazepine?</td>
<td></td>
</tr>
<tr>
<td>- Hypokalaemia (&lt; 3.5 mmol/l)?</td>
<td>(Combination of thiazide and loop diuretic?</td>
<td></td>
</tr>
<tr>
<td>- Hyperkalaemia (&gt; 5.3 mmol/l)?</td>
<td>(Combination of two) potassium-saving diuretics, spironolactone, eplerene, ACE inhibitor, ARB, trimethoprim, NSAID?</td>
<td></td>
</tr>
<tr>
<td>NSAI/renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- (This dose) NSAI necessary?</td>
<td>heart failure, impaired renal function, liver cirrhosis, hypovolaemia</td>
<td>Combination with ACE inhibitor and/or diuretic</td>
</tr>
<tr>
<td>NSAI/ptorie bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- (This dose) NSAI necessary?</td>
<td>&gt;70 years old, ulcer in history, heart failure, diabetes mellitus, severe rheumatism</td>
<td>Combination with coumarin, high therapeutic dose LMWH, SSR, ASA, spironolactone, prednisone</td>
</tr>
<tr>
<td>NSAI otherwise contraindicated?</td>
<td>ulcerative colitis or Crohn’s disease, liver cirrhosis, intercurrent infections, SLE, AR, psoriasis, etc.</td>
<td></td>
</tr>
<tr>
<td>Anticoagulation/antithrombics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Indication vitamin K antagonists?</td>
<td>Associated target value?</td>
<td></td>
</tr>
<tr>
<td>- Pharmacodynamic interaction coumarin, INR value? Bleeding?</td>
<td>Hb values?</td>
<td>Cortmoxazole or other antibiotics, enzyme inhibitors (triazoles omeprazole), enzyme inducers (rifampicne, carbamazepline, phenytyn)</td>
</tr>
<tr>
<td>- Pharmacokinetic interaction coumarin?</td>
<td>NSAID, SSR, prednisone, ASA, ADP receptor antagonists, heparin, antibiotics</td>
<td></td>
</tr>
<tr>
<td>- Perioperative antithrombics correct and according to guidelines?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Indication LMWH? Dose correct?</td>
<td>LMWH prophylactic or therapeutic dose</td>
<td></td>
</tr>
<tr>
<td>- Indication ASA or ADP receptor antagonists?</td>
<td>Combination of ASA + ADP antagonist or with oral anticoagulants?</td>
<td></td>
</tr>
</tbody>
</table>

A multifaceted intervention to reduce drug-related complications in surgical patients

<table>
<thead>
<tr>
<th>Clinical consideration</th>
<th>Relevant conditions</th>
<th>Drugs concerned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Use of opioids?</td>
<td>Stoma, diarrhoea</td>
<td>Short-term use of opioids?</td>
</tr>
<tr>
<td>- Use of opioids?</td>
<td>Consider (risk for) delirium, has an antipsychotic been started?</td>
<td>opiates, especially tramadol relatively contraindicated</td>
</tr>
<tr>
<td>- Use of opioids?</td>
<td>Consider respiratory depression</td>
<td>benzodiazepine?</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Dosing of antibiotics in impaired renal function?</td>
<td></td>
<td>Antibiotics</td>
</tr>
<tr>
<td>- Serum concentrations monitoring necessary?</td>
<td>gentamincis, tobramycin, vancomycin</td>
<td></td>
</tr>
<tr>
<td>- Duration of antibiotic therapy? Intravenous therapy indicated?</td>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>- Allergies?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Perioperative antibiotic prophylaxis indicated?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Endocarditis prophylaxis indicated?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging diagnostics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Radiocrest used?</td>
<td>Renal impairment? Multiple myeloma? Waldenstrom’s disease? Peripheral vascular disease, heart failure, anaemia, age &gt; 75 years, etc.</td>
<td>Combination with diuretics, NSAID, metformin</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Osteoporosis prophylaxis indicated?</td>
<td>Biphosphonates, vitamin D, calcitrene?</td>
<td></td>
</tr>
<tr>
<td>- PPI indicated?</td>
<td>PPI</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Osteoporosis prophylaxis indicated?</td>
<td>Any corticosteroids, anti-androgens, antiepileptics</td>
<td></td>
</tr>
<tr>
<td>- Vitamin D indicated?</td>
<td>antihypertensive agents, diuretics, alpha blockers, or other orthostatic drugs; sedatives (promethazine, codeine, benzodiazepines, barbiturates)</td>
<td></td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Important CYP interactions?</td>
<td>Check on CYP inhibitors, inducers and substrates</td>
<td></td>
</tr>
<tr>
<td>- Risk for QT-prolongation?</td>
<td>Check potassium and magnesium levels</td>
<td>Check on QT prolonging medication</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Indication?</td>
<td>In case of AF, antithrombotics needed?</td>
<td></td>
</tr>
<tr>
<td>- Dose adjustment for renal function and age?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Potassium levels?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A multifaceted intervention to reduce drug-related complications in surgical patients

<table>
<thead>
<tr>
<th>Clinical consideration</th>
<th>Relevant conditions</th>
<th>Drugs concerned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>- Check statins in case of any form of arterial vascular disease</td>
<td>Statin</td>
</tr>
<tr>
<td></td>
<td>- Use of methotrexate?</td>
<td>Supplementation of folic acid</td>
</tr>
<tr>
<td></td>
<td>- Has an antipsychotic been started?</td>
<td>Check on delirium provoking medication (anticholinergics, tramadol, etc.)</td>
</tr>
</tbody>
</table>

ACE inhibitor, angiotensin-converting enzyme inhibitor; ADP receptor antagonist, adenosine diphosphate receptor antagonist; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; ASA, acetylsalicylic acid; INR, international normalised ratio; LMWH, low molecular weight heparin; MDRD, modification of diet in renal disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; SU derivate, sulfonylurea derivate

Appendix 3. Trigger tool used to select patients for potential drug-related events

<table>
<thead>
<tr>
<th>No.</th>
<th>Trigger</th>
<th>Automatic trigger instrument</th>
<th>Modification by research assistant according to protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Readmission within 30 days</td>
<td>Admission in the hospital within 30 days after discharge</td>
<td>Exclusion of planned readmission</td>
</tr>
<tr>
<td>2</td>
<td>Unplanned transfer to ICU/CCU/MCU</td>
<td>Admission to ICU/CCU/MCU</td>
<td>Exclusion of planned admission to ICU/CCU/MCU</td>
</tr>
<tr>
<td>3</td>
<td>Death</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Interdisciplinary consultation</td>
<td>Interdisciplinary consultation</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Bleeding</td>
<td>Use of eptacog alfa</td>
<td>Inclusion of possible medication-related bleeding according protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of high-dose intravenous proton pump inhibitor</td>
<td>Inclusion in case of gastroscopy or colonoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of prothrombin complex</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decrease in haemoglobin of $\geq 3$ mmol/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis code: bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood transfusion</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Probable bleeding</td>
<td>Use of desmopressin in combination with decrease in Hb $\geq 1.5$ mmol/l</td>
<td>Inclusion of possible medication-related bleeding according protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of tranexamic acid in combination with decrease in Hb $\geq 1.5$ mmol/l</td>
<td>Inclusion in case of gastroscopy or colonoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of vitamin K in combination with decrease in Hb $\geq 1.5$ mmol/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia while using methotrexate or co-trimoxazole in combination with decrease in Hb $\geq 1.5$ mmol/l</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Possible heparin-induced thrombocytopenia (HIT)</td>
<td>Use of argatroban, danaparoid</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Thrombo-embolic complication</td>
<td>Diagnosis code: pulmonary embolism or deep venous thrombosis</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Cerebrovascular accident/TIA</td>
<td>Diagnosis code: cerebrovascular accident/TIA</td>
<td>Inclusion of CVA/TIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusion of possible medication-related bleeding according to protocol</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Myocardial ischemia</td>
<td>Diagnosis code: myocardial ischemia</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Hyperkalaemia</td>
<td>Use of polystyrene sulphonate</td>
<td>Inclusion of possible medication-related hyperkalaemia according to protocol</td>
</tr>
</tbody>
</table>
A multifaceted intervention to reduce drug-related complications in surgical patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Trigger</th>
<th>Automatic trigger instrument</th>
<th>Modification by research assistant according to protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Acidosis</td>
<td>pH &lt; 7.3</td>
<td>Inclusion if bicarbonate ≤ 22 mmol/L or PCO₂ ≥ 6 in combination with use of opioids or benzodiazepines</td>
</tr>
<tr>
<td>14</td>
<td>Hypokalaemia</td>
<td>K ≤ 2.5 mmol/L</td>
<td>Inclusion of possible medication-related hypokalaemia according to protocol</td>
</tr>
<tr>
<td>15</td>
<td>Nephrotoxicity</td>
<td>Creatinine rise ≥ 50%</td>
<td>Inclusion of possible medication-related nephrotoxicity according to protocol</td>
</tr>
<tr>
<td>16</td>
<td>Hyponatraemia</td>
<td>pO₂ ≤ 8 kPa (60 mm Hg)</td>
<td>Inclusion of pCO₂ ≥ 6 in combination with use of opioids or benzodiazepines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxygen saturation ≤ 90%</td>
<td>Inclusion in case of chest X-ray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis code: dyspnoea</td>
<td>Inclusion in case of use of diuretic or RAS inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inclusion of infusion or blood transfusion prior to hypoxaemia</td>
</tr>
<tr>
<td>17</td>
<td>Dehydration</td>
<td>Diagnosis code: dehydration</td>
<td>Inclusion of use of diuretics prior to dehydration</td>
</tr>
<tr>
<td>18</td>
<td>Heart failure</td>
<td>Diagnosis code: heart failure</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>Opioid intoxication</td>
<td>Use of naloxone</td>
<td>pCO₂ ≥ 7 in combination with use of opioid</td>
</tr>
<tr>
<td>20</td>
<td>Faecal impaction while using opioid</td>
<td>Laxative or enema in combination with use of opioid</td>
<td>Inclusion of opioid use without laxative</td>
</tr>
<tr>
<td>21</td>
<td>Hypoglycaemia</td>
<td>Glucose ≤ 3 mmol/L</td>
<td>Inclusion of use of insulin or antidiabetic medication</td>
</tr>
<tr>
<td>22</td>
<td>Hypoglycaemia</td>
<td>Glucose ≥ 30 mmol/L</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>Infection</td>
<td>Positive blood culture during admission</td>
<td>Diagnosis code: sepsis</td>
</tr>
<tr>
<td>24</td>
<td>Antibiotics level if deviant from reference</td>
<td>Gentamicin concentration if deviant from reference</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amikacin concentration if deviant from reference</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin concentration if deviant from reference</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tobramycin concentration if deviant from reference</td>
<td>-</td>
</tr>
<tr>
<td>25</td>
<td>Leucopenia while using methotrexate or co-trimoxazole</td>
<td>Leucocytes ≤ 3 x 10⁹/L while using methotrexate or co-trimoxazole</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td>Benzodiazepine intoxication</td>
<td>Use of flumazenil</td>
<td>-</td>
</tr>
<tr>
<td>27</td>
<td>Lithium intoxication</td>
<td>Lithium concentration ≥ 2 mmol/L</td>
<td>-</td>
</tr>
<tr>
<td>28</td>
<td>Digoxin intoxication</td>
<td>Digoxin concentration ≥ 2.5 µg/L</td>
<td>-</td>
</tr>
<tr>
<td>29</td>
<td>Seizure</td>
<td>Use of intravenous or rectal diazepam</td>
<td>-</td>
</tr>
<tr>
<td>30</td>
<td>Concentration of antiepileptic drug deviant from reference</td>
<td>Carbamazepine concentration ≤ 2 mg/L or ≥ 12 mg/L</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valproic acid concentration ≤ 20 mg/L or ≥ 120 mg/L</td>
<td>-</td>
</tr>
</tbody>
</table>

CCU, cardiac care unit; CVA, cerebral vascular accident; ICU, intensive care unit; MCU, medium care unit; TIA, transient ischemic attack
A multifaceted intervention to reduce drug-related complications in surgical patients


Chapter 4

A multifaceted intervention to reduce guideline non-adherence among prescribing physicians in Dutch hospitals

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Peter De Smet
Kees Kramers

Reducing guideline non-adherence among prescribing physicians in Dutch hospitals

Abstract

Background
Despite the potential of clinical practice guidelines to improve patient outcomes, adherence to guidelines by prescribers is inconsistent.

Objective
To determine whether an approach of introducing an educational programme for prescribers in the hospital combined with audit and feedback by the hospital pharmacist reduces non-adherence of prescribing physicians to key pharmacotherapeutic guidelines.

Setting
This prospective intervention study with a before-after design evaluated patients at surgical, urological and orthopaedic wards.

Method
An educational program covering pain management, antithrombotics, fluid and electrolyte management, prescribing in case of renal insufficiency, application of radiographic contrast agents and surgical antibiotic prophylaxis was presented to prescribers on the participating wards. Hospital pharmacists performed medication safety consultations, combining medication review of patients who are at risk for drug related problems with visits to ward physicians.

Main outcome measure
The outcome measure was the proportion of the admissions of patients in which the physician did not adhere to one or more of the included guidelines. Difference was expressed in odds ratios with 95% confidence intervals. Multivariable logistic regression analysis was performed.

Results
1435 Admissions of 1378 patients during the usual care period and 1195 admissions of 1090 patients during the intervention period were included.
Non-adherence was observed significantly less often during the intervention period (21.8% (193/886)) as compared to the usual care period (30.5% (332/1089)). The adjusted odds ratio (OR) was 0.61 (95% CI 0.49-0.76).

Conclusion
This study shows that education and support of the prescribing physician can reduce guideline non-adherence at surgical wards.

Introduction
Preventable, clinically relevant problems due to complex pharmacotherapy are common among hospitalised patients (1-4). Examples are haemorrhage, arterial or venous thrombosis, drug intoxication in renal insufficiency, delirium and faecal impaction. Many of these problems derive from prescribing errors that lead to potentially preventable morbidity, mortality and costs (5). The majority of these are caused by pain medication, antithrombotics, antibacterial drugs, cardiovascular drugs, and drugs that are renally excreted (1-3, 6-9).

Different strategies, including introduction of computerized physician order entry (CPOE), pharmacist involvement on the ward, educational programs and support systems for clinical decision making (CDS) have been studied to address this problem and to improve clinician prescribing in hospitalized patients (10-12).

Clinical practice guidelines with evidence-based recommendations for physicians have been developed to assist doctors and to improve patient outcomes. In routine daily practice however, it appears to be difficult to implement key recommendations and guidelines seem to have limited impact on physician prescribing behaviour. Most clinicians can barely keep pace with the rapid advances in pharmacotherapy. And even if doctors are aware of the guidelines and are willing to change, to alter well established patterns of prescribing is difficult (13). Earlier research showed that non-compliance to several guidelines by prescribers varies between 33 % and 70% (14-16).

Several determinants of practice that prevent or enable guideline adherence, have been described. Guideline factors, such as quality of evidence and accessibility of the guideline, organizational factors and resources, such as the information system, frequent rotations of physicians on the ward and workload, patient factors such as increasingly complex morbidity and also individual health professional factors, such as knowledge and skills, awareness and professional behaviour play a role (17, 18). When these factors are taken into account in the development of strategies to improve guideline adherence, the quality of the treatment of hospitalised patients improves(19, 20).

Education is one of the possible strategies to tackle several of these determinants for non-adherence. Education of prescribers is most effective when it is interactive and continuous, includes discussion of evidence and local consensus and when it is followed by feedback on performance. This way of professional development needs to be built into daily practice however, it appears to be difficult to implement key recommendations and guidelines seem to have limited impact on physician prescribing behaviour. Most clinicians can barely keep pace with the rapid advances in pharmacotherapy. And even if doctors are aware of the guidelines and are willing to change, to alter well established patterns of prescribing is difficult (13). Earlier research showed that non-compliance to several guidelines by prescribers varies between 33 % and 70% (14-16).

Several determinants of practice that prevent or enable guideline adherence, have been described. Guideline factors, such as quality of evidence and accessibility of the guideline, organizational factors and resources, such as the information system, frequent rotations of physicians on the ward and workload, patient factors such as increasingly complex morbidity and also individual health professional factors, such as knowledge and skills, awareness and professional behaviour play a role (17, 18). When these factors are taken into account in the development of strategies to improve guideline adherence, the quality of the treatment of hospitalised patients improves(19, 20).

Education is one of the possible strategies to tackle several of these determinants for non-adherence. Education of prescribers is most effective when it is interactive and continuous, includes discussion of evidence and local consensus and when it is followed by feedback on performance. This way of professional development needs to be built into patient care as much as possible, and should preferably take place in real time with clinical decision-support tools and patient-specific reminders to help doctors make the best decisions (21).

The P-REVIEW study is a prospective, multicentre, open intervention study, designed to investigate if an approach of introducing an educational programme for prescribers in the hospital combined with audit and feedback by the hospital pharmacist can lead to a clinically relevant benefit for patients at surgical wards(22). The educational program teaches the prescriber the pharmacological aspects of using high-risk drugs in high-risk patients. The hospital pharmacist suggests interventions based on a medication review of the patient. Guidelines are an important part of the educational program and the hospital pharmacist actively checks on and improves guideline adherence.
Aim of the study
The aim of the study was to show whether this approach of education combined with structured audit and feedback reduced non-adherence of prescribers to key pharmacotherapeutic guidelines.

Ethics approval
The institutional review boards of the Isala Hospital (Zwolle, the Netherlands) and the Meander Medical Centre (Amersfoort, the Netherlands) stated that the study was exempt from ethical approval. Patients’ data were collected and stored in accordance with prevailing privacy regulations.

Methods
Study design and setting
The P-REVIEW study was an open intervention study with a before-after design performed in two large general teaching hospitals in the Netherlands (the Isala Hospital (779 beds), and the Meander Medical Centre (600 beds)) (22). After a six-month control period (usual care) the intervention was introduced during three months. This was followed by a six-month intervention period. This sub-study on guideline adherence was performed during the fifth month of the usual care period and the fifth month of the intervention period.

Study population
Patients who were admitted to the surgical, urological and orthopaedic wards of the two hospitals during the study period were included. Guideline non-adherence was measured in all these patients. Patients were followed up until discharge. Patients could be included more than once, in case of readmission in the study period. Day care patients were excluded.

Usual care
During the usual care period the normal procedures of medication surveillance and communication between hospital pharmacists and physicians were maintained. A CPOE and CDS system was applied in both hospitals. Hospital pharmacists checked medication of all patients on a daily basis with the aid of computer-generated alerts based on a national database (“G-standard”) (23). They could warn the physician by telephone or in case the advice was less urgent send an advice on paper to the ward. In both hospitals, pharmacists were supported by a same set of computerised “clinical rules” to screen for specific prescribing errors. These clinical rules are based on pharmacotherapeutic guidelines and combine clinical patient data (like renal function and electrolyte abnormalities) with medication specific factors: dose adjustments in case of renal insufficiency; hypokalemia in patients using diuretic; hyperkalemia in patients using potassium-saving diuretics, ACE inhibitor, trimethoprim or NSAID; hyponatremia in patients using SSRI, thiazide or carbamazepine; folic acid to be added to methotrexate; dosing of oral cytostatics; PPI to be added in case of NSAID(24).

Intervention
During the intervention phase, a combination of an educational program and medication counselling for prescribers on the wards took place. An educational program covering pain management, antithrombotics, fluid and electrolyte management, prescribing in the case of renal insufficiency, application of radiographic contrast agents and surgical antibiotic prophylaxis was developed. National and local hospital guidelines related to these subjects were also included (25-32). The program consisted of two parts of approximately two hours each. All prescribers, who provided medical care on the participating wards during the intervention period, attended the course.

Guidelines
In order to be able to score guideline non-adherence ten recommended pharmacotherapeutic measures were derived from several guidelines (Table 1). The guidelines were selected by a group of experts, including hospital pharmacists, clinical pharmacologists and hospital-based physicians in a consensus meeting. The selected guidelines had to relate to medication that has shown to frequently be involved in preventable, clinically relevant, drug-related problems (1-3, 6-8). All guidelines had to be part of a local implemented protocol in the hospital and were addressed in the educational program.
Reducing guideline non-adherence among prescribing physicians in Dutch hospitals

Study endpoints
The primary outcome measure of guideline non-adherence was the proportion of the admissions of patients in which the physician did not adhere to one or more of the guidelines. The secondary outcome measures were the proportions of admissions of patients in which the physician did not adhere to each of ten guidelines.

Data collection
Collected data included patient characteristics, laboratory and medication data, as well as transfers to other wards, medical correspondence and medical interventions. Data regarding radiology, microbiology, blood transfusion and information about medical incidents were also collected. Part of the requisite data could not be collected automatically. Therefore, a trained research assistant collected data manually from the medical records of the patients using a predefined protocol. These data included whether the patient had had surgery, type of surgery and whether the patient had an indication for thrombosis prophylaxis, antibiotics prophylaxis or endocarditis prophylaxis. A validated multisource Microsoft Access database (Microsoft version 2003) was used.

Sample size and data analysis
The PREVIEW-study has been powered on the outcome measure of reduction of clinically relevant, potentially preventable drug-related problems. For the power of this sub-study on guideline adherence, we studied earlier research on this subject showing that non-compliance to several guidelines by prescribers varies between 33 % and 70%(14-16). Earlier studies that describe interventions that aim to improve guideline adherence showed results on improvement of adherence varying from 50-60% to 65-80% (19, 20). To detect a reduction from 30 % non-adherence to 20% non-adherence, 313 patients had to be included in each group. Because the primary outcome measure of the P-REVIEW study (adverse drug events) needed a very large patient cohort to detect a significant difference, we assumed that measuring during one month in both periods would generate enough power for this sub-study on guideline adherence.

Differences between groups were expressed in odds ratios with 95% confidence intervals and were tested for statistical significance using independent t-test or chi-square tests, as appropriate. P < 0.05 was considered to be statistically significant. In order to correct for possible confounding, multivariable logistic regression analysis was performed. The following possible confounders were initially entered into the model: age, gender, department of admission, number of medicines on the first day after admission and pharmacotherapeutic group of these medicines, length of stay and renal function. Those that showed no clear relation with the outcome (P>0.10) were removed, but only in case their removal did not alter the relation under study (OR on non-adherence in usual care period vs intervention period) by more than 10%. Statistical analyses were performed using SPSS Statistics version 22 (IBM Software, New York).

Table 1. Pharmacotherapeutic measures based on prevailing guidelines

<table>
<thead>
<tr>
<th>Pharmacotherapeutic measure</th>
<th>Effectuation measurement of guideline non-adherence</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Perioperative thrombosis prophylaxis</td>
<td>All patients undergoing surgery, with a high risk of thrombosis according to the guideline, were checked whether preventive therapy for DVT and VTE was administered.</td>
<td>Diagnostics, prevention and treatment of venous thromboembolism and secondary prevention of arterial occlusive disease (guideline CBO, based on ACCP)(25)</td>
</tr>
<tr>
<td>2. Perioperative bridging of antithrombotics</td>
<td>All patients undergoing surgery, using vitamin K Antagonists, were checked whether perioperative bridging of antithrombotics was indicated and antithrombotics were administered according to the guideline. Bridging was indicated in case of atrial fibrillation and a CHADS2 score &gt; 1, recent or recurrent venous thromboembolism, thromboembolism due to thrombophilia or mechanical valve prosthesis.</td>
<td>Diagnostics, prevention and treatment of venous thromboembolism and secondary prevention of arterial occlusive disease (guideline CBO, based on ACCP)(25)</td>
</tr>
<tr>
<td>3. PPI added in case of use of NSAID</td>
<td>All patients with an ulcer in history and/or an age older than 70 years, were checked whether a proton pump inhibitor was added.</td>
<td>NSAID use and prevention of gastric damage (guideline CBO) (26)</td>
</tr>
<tr>
<td>4. Laxative added in case of use of opioid</td>
<td>All patients treated with an opioid, were checked whether a laxative was added. Patients with a stoma or with diagnosed diarrhoea were excluded.</td>
<td>Pain (guideline NHG) (27), Diagnostics and treatment of pain (guideline Oncoline) (28)</td>
</tr>
<tr>
<td>5. NSAID contraindicated in impaired renal function</td>
<td>All patients with an impaired renal function (MDRD &lt;30 ml/min/1.73m2), were checked for NSAID use.</td>
<td>Dutch national G-standard (23), SmPC NSAID(29)</td>
</tr>
<tr>
<td>6. Discontinuation of diuretics in case of radiocontrast</td>
<td>All patients who received iodinated radio-contrast and who used diuretics, were checked whether the diuretic was discontinued on the day of the test.</td>
<td>Precautions for use of iodinated radio-contrast (guideline NVR) (30)</td>
</tr>
<tr>
<td>7. Discontinuation of NSAID in case of radiocontrast</td>
<td>All patients who received iodinated radio-contrast and who used an NSAID, were checked whether the NSAID was discontinued on the day of the test.</td>
<td>Precautions for use of iodinated radio-contrast (guideline NVR)(30)</td>
</tr>
<tr>
<td>8. Discontinuation of metformin in case of radiocontrast and impaired renal function</td>
<td>All patients who received iodinated radio-contrast and had impaired renal function (MDRD &lt;60 ml/min/1.73m2) and used metformin, were checked whether metformin was discontinued on the day of the test.</td>
<td>Precautions for use of iodinated radio-contrast (guideline NVR)(30)</td>
</tr>
<tr>
<td>9. Perioperative antibiotics prophylaxis</td>
<td>All patients undergoing surgery, with an indication for perioperative antibiotics prophylaxis, were checked whether preventive therapy for infection was administered.</td>
<td>Perioperative antibiotic prophylaxis (guideline SWAB)(31)</td>
</tr>
<tr>
<td>10. Perioperative endocarditis prophylaxis</td>
<td>All patients undergoing surgery, with a high risk of endocarditis, were checked whether preventive therapy for endocarditis was administered.</td>
<td>Endocarditis prophylaxis (guideline by the Nederland Heart Foundation) (32)</td>
</tr>
</tbody>
</table>

ACCP, American College of Chest Physicians; CBO, Dutch Institute for Health Care Improvement; DVT, deep vein thrombosis; MDRD, modification of diet in renal disease; NHG, Dutch Society of General Practitioners; NSAID, non-steroidal anti-inflammatory drug; NVR, Dutch Association of Radiology; PPI, proton pump inhibitor; SmPC, Summary of Product Characteristics; SWAB, The Dutch Working Party on Antibiotic Policy; VTE, venous thromboembolism.
Results
In the usual care period of the study 1435 admissions (1378 patients) and in the intervention period 1195 admissions (1090 patients) were included. Table 2 details the characteristics of these patients. There was no difference between the two groups in age, gender, department of admission or in the number of medications on the first day after admission. Also, there was no difference in use of medication, length of hospital stay and the proportion of patients with renal insufficiency.

Table 2. Characteristics of admitted patients

<table>
<thead>
<tr>
<th></th>
<th>Usual care period</th>
<th>Intervention period</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of admissions</td>
<td>1435</td>
<td>1195</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>1378</td>
<td>1090</td>
<td></td>
</tr>
<tr>
<td>Mean age of patients in years ± SD</td>
<td>63.8 ± 17.2</td>
<td>63.3 ± 17.1</td>
<td>0.406</td>
</tr>
<tr>
<td>Gender of patients, n (%) female</td>
<td>720 (50.2 %)</td>
<td>599 (50.1 %)</td>
<td>0.980</td>
</tr>
<tr>
<td>Department of admission</td>
<td></td>
<td></td>
<td>0.605</td>
</tr>
<tr>
<td>- General surgery, n (%)</td>
<td>852 (59.4%)</td>
<td>682 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>- Orthopaedic surgery, n (%)</td>
<td>328 (22.9%)</td>
<td>294 (24.6%)</td>
<td></td>
</tr>
<tr>
<td>- Urology, n (%)</td>
<td>255 (17.8%)</td>
<td>219 (18.3%)</td>
<td></td>
</tr>
<tr>
<td>Mean no. of medications the first day after admission, ± SD</td>
<td>6.9 ± 5.5</td>
<td>7.2 ± 5.8</td>
<td>0.233</td>
</tr>
</tbody>
</table>

Medication the first day after admission, n (%)

- Hypoglycemics: 178 (12.4%) vs. 156 (13.1%), p = 0.618
- Vitamin K antagonists: 149 (10.4%) vs. 117 (9.8%), p = 0.616
- Heparin/LMWH: 951 (66.3%) vs. 773 (64.7%), p = 0.394
- Thrombocyte aggregation inhibitors: 284 (19.8%) vs. 238 (19.9%), p = 0.936
- Diuretics: 337 (23.5%) vs. 287 (24.0%), p = 0.749
- Beta blockers: 391 (27.2%) vs. 305 (25.3%), p = 0.318
- Calcium channel blockers: 146 (10.2%) vs. 142 (11.9%), p = 0.162
- RAS inhibitors: 375 (26.1%) vs. 317 (26.5%), p = 0.819
- NSAIDs: 485 (33.8%) vs. 424 (35.5%), p = 0.366
- Opioids: 601 (41.9%) vs. 491 (41.1%), p = 0.681
- Antipsychotics: 90 (6.3%) vs. 79 (6.6%), p = 0.724

Mean length of stay, days ± SD

- General surgery: 7.7 ± 9.7 vs. 7.0 ± 8.3, p = 0.154
- Orthopaedic surgery: 7.6 ± 8.6 vs. 6.7 ± 6.5, p = 0.107
- Urology: 6.3 ± 6.8 vs. 4.4 ± 4.1, p = 0.798

MDRD eGFR of patients (ml/min/1.73 m²), n (%) (n = 1016*) vs. (n = 836*) = 0.476

- <10: 4 (0.4%) vs. 1 (0.1%)
- 10-30: 43 (4.2%) vs. 39 (4.7%)
- 30-60: 227 (22.3%) vs. 203 (24.3%)
- >60: 742 (73.0%) vs. 593 (70.9%)

LMWH = Low molecular weight heparin; RAS = Renin angiotensin system; NSAIDs = Non-steroidal anti-inflammatory drugs

Reducing guideline non-adherence among prescribing physicians in Dutch hospitals

Table 3 shows the proportions of admissions of patients in which the physician did not adhere to the guidelines in the usual care period and in the intervention period, respectively. In 1089 admissions of 1069 patients in the usual care period and in 886 admissions of 864 patients in the intervention period, one or more included guidelines were applicable.

Table 3. Non-adherence of prescribers to pharmacotherapeutic measures based on prevailing guidelines

<table>
<thead>
<tr>
<th></th>
<th>Usual care period (n = 1435)</th>
<th>Intervention period (n = 1195)</th>
<th>Odds ratios and confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-adherence</td>
<td>Non-adherence</td>
<td>OR</td>
</tr>
<tr>
<td>1. Perioperative thrombosis prophylaxis if indicated?</td>
<td>22/590 (3.7%)</td>
<td>10/490 (2.0%)</td>
<td>0.54</td>
</tr>
<tr>
<td>2. Perioperative bridging of antithrombotics if indicated?</td>
<td>2/48 (4.2%)</td>
<td>2/46 (4.3%)</td>
<td>1.05</td>
</tr>
<tr>
<td>3. In case of NSAID use, ppi added if indicated?</td>
<td>5/101 (5.0%)</td>
<td>3/83 (3.6%)</td>
<td>0.72</td>
</tr>
<tr>
<td>4. In case of opioid use, laxative added if indicated?</td>
<td>154/296 (52%)</td>
<td>62/190 (32.6%)</td>
<td>0.45*</td>
</tr>
<tr>
<td>5. In case of impaired renal function (MDRD &lt;30), no use of NSAID?</td>
<td>8/50 (16.0%)</td>
<td>4/40 (10.0%)</td>
<td>0.54</td>
</tr>
<tr>
<td>6. In case of radiocontrast, diuretics discontinued?</td>
<td>16/23 (69.6%)</td>
<td>20/29 (69.0%)</td>
<td>0.97</td>
</tr>
<tr>
<td>7. In case of radiocontrast, NSAID discontinued?</td>
<td>17/25 (68.0%)</td>
<td>15/20 (75.0%)</td>
<td>1.41</td>
</tr>
<tr>
<td>8. In case of radiocontrast and MDRD &lt; 60, metformin discontinued?</td>
<td>2/3 (66.7%)</td>
<td>2/2 (100.0%)</td>
<td>0.33</td>
</tr>
<tr>
<td>9. Perioperative antibiotics prophylaxis, if indicated?</td>
<td>136/832 (16.3%)</td>
<td>93/661 (14.1%)</td>
<td>0.84</td>
</tr>
<tr>
<td>10. Perioperative endocarditis prophylaxis, if indicated?</td>
<td>6/8 (75%)</td>
<td>0/3 (0%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Overall non-adherence</td>
<td>332/1089 (30.5%)</td>
<td>193/886 (21.8%)</td>
<td>0.64*</td>
</tr>
</tbody>
</table>

OR, adjusted for confounders, *statistical significant
Figure 1. shows a forest plot in which the odds ratios for non-adherence are presented.

Figure 1. Forest plot of non-adherence of prescribers to pharmacotherapeutic measures based on prevailing guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>OR Guideline</th>
<th>OR 95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative thrombosis</td>
<td>0.54</td>
<td>[0.25, 1.15]</td>
</tr>
<tr>
<td>Perioperative bridging</td>
<td>1.05</td>
<td>[0.14, 7.75]</td>
</tr>
<tr>
<td>NSAID use: PPI added</td>
<td>0.72</td>
<td>[0.17, 3.11]</td>
</tr>
<tr>
<td>Opioid use: laxative added</td>
<td>0.45</td>
<td>[0.31, 0.65]</td>
</tr>
<tr>
<td>Impaired renal function: no use of NSAID</td>
<td>0.54</td>
<td>[0.15, 1.94]</td>
</tr>
<tr>
<td>Radiocontrast: diuretics discontinued</td>
<td>0.97</td>
<td>[0.30, 3.18]</td>
</tr>
<tr>
<td>Radiocontrast: NSAID discontinued</td>
<td>1.41</td>
<td>[0.38, 5.26]</td>
</tr>
<tr>
<td>Radiocontrast: metformin discontinued</td>
<td>0.33</td>
<td>[0.01, 12.79]</td>
</tr>
<tr>
<td>Perioperative antibiotics prophylaxis</td>
<td>0.94</td>
<td>[0.63, 1.32]</td>
</tr>
<tr>
<td>Perioperative endocarditis prophylaxis</td>
<td>0.05</td>
<td>[0.00, 1.50]</td>
</tr>
<tr>
<td>OVERALL</td>
<td>0.61</td>
<td>[0.49, 0.76]</td>
</tr>
</tbody>
</table>

A significantly lower proportion of admissions of patients in which the physician did not adhere to the prevailing guidelines occurred in the intervention period (21.8% (193/886) compared to the usual care period (30.5% (332/1089)) (p<0.05). The odds ratio (OR) was 0.64 (95% CI 0.52-0.78).

After correction for possible confounders, the adjusted OR was 0.61 (95% CI 0.49-0.76). When the analysis was conducted with protocol non-adherence as denominator (total number of times that a guideline had to be followed by a prescriber) instead of admissions, results were comparable. (13.5% (211/1564) in the intervention period compared to 18.6% (368/1976) in the usual care period (p<0.05)). The odds ratio (OR) was 0.68 (95% CI 0.57-0.82).

Discussion

Our study shows that education and support of the prescribing physician with respect to high-risk patients in surgical departments can lead to reduced pharmacotherapeutic guideline non-adherence among prescribing physicians. Achieved effects were obtained on top of the effect of other measures as CPOE/CDS system and clinical rules, which were part of usual care.

Earlier studies describe interventions that aim to improve guideline adherence in the hospital. Hogli et al. describe an intervention study, reporting distribution of a recently published pocket version of the national guideline. This led to a substantial increase in prescribing of appropriate empirical antibiotics from 61.7 to 83.8% (20). Schouten et al. implemented a multifaceted guideline-implementation strategy, considering the barriers of implementation of guidelines. They found an increase of the rate of guideline adherence of antibiotic prescription from 50.3% to 64.3% (19).

In the two hospitals that participated in this study, the guidelines targeted in our study had already been implemented. Nevertheless, we found that in nearly one third of cases physicians were non-adherent to the local hospital guidelines. This is in line with earlier research on this subject. Van den Bemt et al. found that the proportion of admissions not compliant with guidelines on gastric protection in case of use of NSAID in hospitalized surgical patients was 46.6% (16). Drenth et al. found an adherence of 53.9% with a dosing guideline in patients with impaired renal function at hospital discharge (15). Schilp et al. studied adherence to the guideline concerning identification and hydration of high-risk patients for contrast-induced nephropathy in different hospitals and found that only two third of the high-risk patients were hydrated before contrast administration (33).

Educating prescribers is a measure that can be taken on top of other measures to improve guideline adherence. Educating prescribers is only effective if it is a part of a multifaceted intervention (35). Novel of the P-REVIEW education program is the combination with a weekly visit by the hospital pharmacist, who audited and improved guideline adherence. We aimed to boost the effect of the education program by the weekly visits of the hospital pharmacist. We previously showed that these weekly visits were feasible and also efficient. We hypothesized that the support by education of the prescriber by the hospital pharmacist in a more pro-active role is more efficient and effective than the traditional retrospective role of the hospital pharmacist in medication surveillance (22). In this study we show that this intervention can lead to a significant decrease in non-adherence of guidelines, although there may be still room for improvement.

The study has several strengths. The study was performed in two representative general teaching hospitals. The intervention was easily implemented, since both education and weekly visits were performed by health care providers already active in the hospital and the intervention did not lead to additional costs.
The intervention combines different strategies. These strategies address different factors that have been described to impair quality of care and can influence guideline adherence (17).

By educating the prescriber in the hospital and teaching the prescriber during medication safety consultation, the knowledge and skills needed to adhere to guidelines will improve. Also the attitude towards guidelines in general and motivation to adhere may improve. This study however, didn’t collect qualitative data from the prescribers to support this hypothesis, and this would be useful to integrate in future research.

These weekly visits of the hospital pharmacist can be considered as a continuous form of workplace-based education. This addresses the problem that a short-term education programme has been found to have only a transient effect on the frequency of prescribing errors (36).

There are some limitations as well. We selected ten relevant pharmacotherapeutic measures derived from several guidelines. This selection was not complete, and our results may not be generalisable to other or all guidelines. Also, the study was performed in two hospitals, which might limit the external validity of the study.

This study was not a randomised controlled study, but was performed in a before after design, introducing the possibility of confounding. Therefore, to adjust for confounding, we performed a multivariable logistic regression analysis. Yet, we may not have identified all potential confounders.

We defined the outcome measure as the proportion of the admissions of patients in which the physician did not adhere to one or more of the guidelines. We assumed that in every single admission a physician has to follow all guidelines. When a patient is readmitted, the treating physician is often different and guidelines can be different from an early admission of the patient. On the other hand adherence on guidelines in an early admission can lead to (not intended) adherence in a readmission.

For each guideline we only included these cases in which there was no possible discussion on adherence (table 1). By specifying the cases, we minimized the possibility of intended non-adherence by the physician.

The P-REVIEW study describes 106 admissions with one or more clinically relevant, potentially preventable, drug-related events in the usual care period and 73 in the intervention period (22). These drug-related events are divided into different types of events, such as haemorrhage, thrombosis, renal failure related events, central nervous systems events, faecal impaction, hypoventilation and a group of unclassifiable events (22). We noted that 25 of the 106 events in the usual care period and 15 of the 73 events in the intervention period relate to the studied guidelines and could possibly have been prevented in case of better guideline adherence. That means that only a modest part of the positive effect on these events can be related to an improvement in adherence of the studied guidelines.

This suggests that improving guideline adherence will have only limited effect and it may not be necessary to pursue 100% adherence. It may be better not to focus on guideline adherence or implementation of clinical rules alone, but on a comprehensive medication review of high risk patients, in which a check on adherence of guidelines and clinical rules is integrated.

Given the limited resources in healthcare, we think this could be an important question for future research.

Conclusions

In summary, this study shows that education and support of the prescribing physician with respect to high-risk patients in surgical departments leads to an improvement of guideline adherence among prescribing physicians.

Acknowledgements

We would like to express our gratitude to the hospital pharmacists and to the physicians of the surgical, orthopaedic surgical and urological wards of the Meander Medical Centre in Amersfoort and the Isala Hospital in Zwolle.
References

Chapter 5

Prediction of clinically relevant adverse drug events in surgical patients

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PLoS One 2018; revision under review
Abstract

Background
Risk stratification of hospital patients for adverse drug events (ADE) would enable targeting patients who may benefit from interventions aimed at reducing drug-related morbidity. It would support clinicians and hospital pharmacists in selecting patients to deliver a more efficient health care service. This study aimed to develop and test a prediction model that helps to identify patients on the day of hospital admission who are at increased risk of developing a clinically relevant, preventable adverse drug event during their stay on a surgical ward.

Methods
Data of the pre-intervention measurement period of the P-REVIEW study were used. This study was designed to assess the impact of a multifaceted educational intervention on clinically relevant, preventable adverse drug events in surgical patients. Thirty-nine variables were evaluated in a univariate and multivariate logistic regression analysis, respectively. Model performance was expressed in the Area Under the Receiver Operating Characteristics (AUROC). Bootstrapping was used for model validation.

Results
6780 admissions of patients at surgical wards were included during the pre-intervention period of the PREVIEW trial. 102 Patients experienced a clinically relevant, adverse drug event during their hospital stay that was deemed potentially preventable. The prediction model comprised five variables, each ascertained at the time of hospital admission: age, number of biochemical tests ordered, heparin/LMWH in therapeutic dose, use of opioids and use of cardiovascular drugs. The AUROC was 0.86 (95% CI 0.83-0.88). At a cut-off point for an increased risk of developing an ADE of 1.6%, the model had a sensitivity of 80.4% and a specificity of 73.4%. The positive and negative predictive value were 4.5% and 99.6%, respectively. The bootstrap procedure did not significantly affect model parameters.

Conclusion
The combined use of a limited set of easily ascertainable patient characteristics can help physicians and pharmacists to identify, at the time of admission, surgical patients who are at increased risk of developing ADEs during their hospital stay. This may serve as a basis to take extra precautions to safeguard medication safety in those patients.

Introduction
Pharmacotherapy is one of the most commonly applied interventions in hospital healthcare. In addition to the beneficial effects, prescribing of medication also introduces risks of medication errors and adverse drug events, that lead to potentially preventable morbidity, mortality and costs(1-3). Especially patients on surgical wards are at risk, due to need for pain medication and antibiotics, frequent adjustments of antithrombotic regimens and blood and fluid loss. In the case of elderly surgical patients, multiple co-morbidities requiring multiple drugs add even more to potential drug-related problems (4).

Risk prediction is a routine component in daily care practice in both specific areas (e.g. approaches used to determine stroke risk in patients with atrial fibrillation) as well as more generally, for example to identify patients at risk of hospital admission. Risk stratification of hospital patients for adverse drug events (ADE) can target a population that can benefit from interventions aimed to reduce drug-related morbidity, as a form of personalized medicine. It can support clinicians and hospital pharmacists in patient prioritization to deliver a more efficient health care service (5). Yourman et al. emphasized in a systematic review that failure to consider risk prediction in a clinical setting can result in poor patient outcome (6).

A recent review identified four studies that developed and validated ADE risk-prediction tools for use in adults over 65 years of age (4, 5, 7-9). These prediction models had poor to modest performance and did not address clinical impact, thereby limiting clinical usefulness. Because a large number of variables contribute to ADE occurrence in patients, it is impossible to precisely predict every ADE in every patient. Therefore, Stevenson et al. suggested that these risk prediction strategies should focus either on one specific harmful ADE (e.g. gastrointestinal or intracranial bleeding) or ADEs in patients with a particular illness or clinical characteristic, for instance surgical patients (5). In addition, since the aim is to prevent patient harm, it seems more rational to predict clinically relevant, potentially preventable adverse events, instead of adverse reactions in general.

The P-REVIEW study (Pharmacist-led Risk patients medication Evaluation to Initiate Event reduction on surgical Wards) was designed to determine whether a multifaceted intervention of educating the prescriber combined with medication review and pharmaceutical visits to the ward by the hospital pharmacist could lead to a reduction of drug-related complications among surgical patients (10). In this study, experts assessed clinically relevant, potentially preventable ADE (leading to death, temporary or sustained disability, increased length of hospital stay or readmission within 30 days) in a cohort of 13,264 admissions of surgical patients. The study showed a significant benefit for patients in the intervention period. To improve the cost effectiveness of medication review and other measures to prevent avoidable harm, it would be useful to identify the patients at risk of clinically relevant ADEs at the surgical ward. For this purpose, we used the P-REVIEW data to develop a risk-prediction model that could identify patients at risk of a clinically relevant, potentially preventable adverse drug event during admission at the surgical ward, on the day of hospital admission.
Methods

Study setting and population
The P-REVIEW study is a prospective open intervention study designed to investigate whether a multifaceted educational intervention could lead to a reduction of clinically relevant, potentially preventable adverse drug events among patients at surgical wards. The study was performed in two large general teaching hospitals in the Netherlands and has been described in detail elsewhere (10). Patients who were admitted to the surgical, urological or orthopaedic ward of one of the two hospitals during a period of six months were included. In case of readmission, patients could be included more than once. Day care patients were excluded. For the development of the prediction model, data were used from patients during the pre-intervention period.

P-REVIEW data set and clinically relevant potentially preventable adverse drug events
Data available in the P-REVIEW dataset were collected for each admission, including patient characteristics, drug history and biochemical, haematological and microbiological markers. The major part of the data collection was performed automatically from the CPOE system (computerized physician order entry). In addition, some of the data were collected manually by a review of the medical records.

Data from the day of admission of each patient was extracted. If more (laboratory) values were available of the same variable, the last one, being the most recent value available, was extracted.

Assessment of clinically relevant, potentially preventable adverse drug events that led to death, temporary or permanent disability, increased length of hospital stay or readmission within 30 days was performed in the P-REVIEW study by teams of experts consisting of a hospital pharmacist and a hospital-based physician, not related to the study hospitals (10).

Predicting variables
From the data that were collected in the P-REVIEW study, candidate model parameters were selected on the basis of reports in the literature of their association with ADEs (1-4, 11-18). Thirty-nine risk factors were identified, including patient characteristics (age, gender), department of admission (general surgery versus orthopaedic surgery and urology), type of admission (emergency versus elective); medication (number of medications, use of gastrointestinal drugs, hypoglycemic drugs, vitamin K antagonists, heparin or low molecular weight heparin (LMWH) in therapeutic dose, thrombocyte aggregation inhibitors, cardiovascular drugs in general, cardiac drugs, diuretics, beta-blockers, renin angiotensin system (RAS) inhibitors, antilipaemica, corticosteroids, antimicrobials, chemotherapy, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, antiepileptics, central nervous system (CNS) agents in general, antipsychotics, anxiolytics, antidepressants and serious drug-drug interactions); laboratory test results (albumin, glucose, hemoglobin, international normalized ratio (INR), potassium, sodium, leucocytes, chronic kidney disease epidemiology (CKD-EPI), oxygen saturation, positive microbiological blood culture, number of biochemical tests ordered (<20 versus ≥20)); (1-4, 11-18). Drugs were coded according to the Anatomical Therapeutic and Chemical codes (19). The glomerular filtration rate was computed by the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI)(20). Missing data where imputed using the ‘multiple imputation’ procedure from SPSS version 22. SPSS uses a Markov Chain Monte Carlo (MCMC) algorithm known as Fully Conditional Specification (FCS). This method can be used when the pattern of missing data is arbitrary. For each iteration and for each variable in the order specified in the variable list, the FCS method fits a univariate (single dependent variable) model using all other available variables in the model as predictors. Linear regression was used to predict a scale variable and logistic regression to predict categorical variables. Variables of which more than 60% of data were missing were left out of the analysis.

Model development
Model development consisted of two stages (21). In the first stage, possible predictors were tested using a univariate binary logistic regression model. Variables that were found to be statistically significant (P<0.05) were taken forward to the next stage of multivariate analysis.

In case of (laboratory) variables that in clinical practice can be either too high or too low and confer a risk in both situations, categorization of variables was performed (for instance, low potassium values < 3.5 mmol/l, normal values between 3.5 and 5.0 mmol/l and high values > 5.0 mmol/l).

In the second stage, backward and forward elimination procedures were used in multivariate logistic regression analysis in order to detect the best predictors. The removal criterion was set at p=0.10.

Results from the univariate and multivariate logistic regression models were expressed in terms of the odds ratio with 95% confidence intervals and p-values.

Standardized odd ratios were computed to allow for comparison of the strength of the association between the various continuous variables and the probability of an ADE. Standardization was achieved through Z-transformation.

Model performance
Model performance of the logistic regression model was expressed in the Area Under the Curve (AUC) as computed by a Receiver Operating Characteristics curve analysis (ROC analysis) using the probability as predicted by the regression model and the real outcome (ADE).

Model validation
Bootstrap was used to assess the internal validity of the model. Two hundred bootstrap samples were drawn to assess the reliability of the model expressed in over-optimism and the uniform shrinkage factor.

Statistical analyses were performed using SPSS Statistics version 22 (IBM Software, New York). Bootstraping was performed in SAS version 9.4.

Ethics
For all stages of this research, patient records were anonymized prior to analysis in accordance with prevailing privacy regulations.
Results
The pre-intervention period of the P-REVIEW dataset study population comprised 6780 admissions of 5940 patients at surgical wards. A clinically relevant, potentially preventable adverse drug event during hospital stay, that had led to death, temporary or permanent disability, increased length of hospital stay or readmission within 30 days was determined in 102 patients. The most frequent types of events were haemorrhage, arterial or venous thrombosis, renal insufficiency, dehydration or electrolyte related events, central nervous system events and faecal impaction. Characteristics of patients who did, and who did not experience an ADE during hospital stay are shown in Table 1.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Admissions with a clinically relevant ADE (n=102)</th>
<th>Admissions without a clinically relevant ADE (n=6678)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of patients in years ± SD</td>
<td></td>
</tr>
<tr>
<td>78.7 ± 8.7</td>
<td>63.1 ± 17.6</td>
</tr>
<tr>
<td>Gender of patients, n (%) female</td>
<td></td>
</tr>
<tr>
<td>50 (49.0%)</td>
<td>3331 (49.9%)</td>
</tr>
<tr>
<td>Department of admission, n (%)</td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td></td>
</tr>
<tr>
<td>67 (65.7%)</td>
<td>3824 (57.3%)</td>
</tr>
<tr>
<td>Urology</td>
<td></td>
</tr>
<tr>
<td>4 (3.9%)</td>
<td>1244 (18.6%)</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td></td>
</tr>
<tr>
<td>31 (30.4%)</td>
<td>1610 (24.1%)</td>
</tr>
<tr>
<td>Admission, n (%) elective</td>
<td></td>
</tr>
<tr>
<td>39 (38.2%)</td>
<td>4194 (62.8%)</td>
</tr>
<tr>
<td>No. of medications (mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>11.1 ± 4.8</td>
<td>6.6 ± 5.5</td>
</tr>
</tbody>
</table>

Table 2. Candidate predictive variables

<table>
<thead>
<tr>
<th>Predictive variables (references)</th>
<th>N missing (%)</th>
<th>OR</th>
<th>CI</th>
<th>P-value</th>
<th>Standardized OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0 (0)</td>
<td>1.09</td>
<td>1.07 - 1.09</td>
<td>&lt;0.0001</td>
<td>4.33 (1.11 - 6.03)</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>0 (0)</td>
<td>0.97</td>
<td>0.65 - 1.43</td>
<td>0.862</td>
<td></td>
</tr>
<tr>
<td>Department of admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Surgery vs Urology</td>
<td>204 (3.1)</td>
<td>4.95</td>
<td>1.79 - 13.65</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Orthopedic S vs Urology</td>
<td>5.89</td>
<td>2.07 - 16.28</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission (emergency vs elective)</td>
<td>235 (3.5)</td>
<td>2.91</td>
<td>1.94 - 4.37</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Medication use (ATC code)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of medications</td>
<td>0 (0)</td>
<td>1.13</td>
<td>1.10 - 1.16</td>
<td>&lt;0.0001</td>
<td>1.94 (1.65 - 2.29)</td>
</tr>
<tr>
<td>Serious drug-drug interactions</td>
<td>0 (0)</td>
<td>3.99</td>
<td>2.20 - 7.24</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal drugs (A02)</td>
<td>0 (0)</td>
<td>1.60</td>
<td>1.08 - 2.37</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemics (A10)</td>
<td>0 (0)</td>
<td>3.17</td>
<td>2.04 - 4.93</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Vitamin K antagonists (B01AA)</td>
<td>0 (0)</td>
<td>2.03</td>
<td>1.04 - 3.90</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>Heparin/LMWH in therapeutic dose (B01AB)</td>
<td>0 (0)</td>
<td>4.23</td>
<td>2.37 - 7.55</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Thrombocyte aggregation inhibitors (B01AC)</td>
<td>0 (0)</td>
<td>3.21</td>
<td>2.14 - 4.82</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular drugs (C)</td>
<td>0 (0)</td>
<td>9.21</td>
<td>5.29 - 16.38</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Cardiac drugs (C01)</td>
<td>0 (0)</td>
<td>3.55</td>
<td>2.23 - 5.65</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diuretics (C03)</td>
<td>0 (0)</td>
<td>3.70</td>
<td>2.50 - 5.49</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Betablockers (C07)</td>
<td>0 (0)</td>
<td>3.35</td>
<td>2.26 - 4.76</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>RAS inhibitors (C09)</td>
<td>0 (0)</td>
<td>3.15</td>
<td>2.12 - 4.66</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Antilipaemicae (C10)</td>
<td>0 (0)</td>
<td>2.36</td>
<td>1.58 - 3.55</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids (H02)</td>
<td>0 (0)</td>
<td>2.01</td>
<td>0.92 - 4.38</td>
<td>0.078</td>
<td></td>
</tr>
<tr>
<td>Antimicrobials (J01,J02)</td>
<td>0 (0)</td>
<td>1.73</td>
<td>1.17 - 2.56</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (L01)</td>
<td>0 (0)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs (M01A)</td>
<td>0 (0)</td>
<td>0.71</td>
<td>0.45 - 1.13</td>
<td>0.149</td>
<td></td>
</tr>
<tr>
<td>Opioids (N02A)</td>
<td>0 (0)</td>
<td>4.39</td>
<td>2.90 - 6.65</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Antiepileptics (N03)</td>
<td>0 (0)</td>
<td>1.59</td>
<td>0.69 - 3.67</td>
<td>0.273</td>
<td></td>
</tr>
<tr>
<td>CNS agents (N05,N06)</td>
<td>0 (0)</td>
<td>4.91</td>
<td>2.70 - 8.94</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics (N05A)</td>
<td>0 (0)</td>
<td>1.65</td>
<td>1.10 - 2.48</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Anxiolytics (N05B)</td>
<td>0 (0)</td>
<td>1.59</td>
<td>0.84 - 2.99</td>
<td>0.153</td>
<td></td>
</tr>
<tr>
<td>Antidepressants (N06A)</td>
<td>0 (0)</td>
<td>1.71</td>
<td>0.93 - 3.14</td>
<td>0.066</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>5839 (86.1)</td>
<td>0.96</td>
<td>0.92 - 1.00</td>
<td>0.055</td>
<td>0.74 (0.54 - 1.01)</td>
</tr>
</tbody>
</table>

Univariate analysis
The candidate predictive variables of a clinically relevant ADE during hospital stay and results of the univariate analysis are reported in Table 2.
Univariate analysis | Standardized OR
--- | ---
Predictive variables (references) | N missing (%) | OR | CI | P-value | OR (95% CI)
Glucose (mmol/L) | 5097 (75.2) | 1.14 | 1.04 – 1.24 | 0.004 | 1.40 (1.11 – 1.77)
Hemoglobin (mmol/L) | 3901 (57.5) | 2.83 | 1.48 – 5.43 | 0.002 | 1.08 (0.83 – 1.39)
INR (ratio) | 5775 (85.2) | 1.07 | 0.84 – 1.36 | 0.582 | 1.08 (0.83 – 1.39)
Potassium (mmol/L) | 3085 (45.5) | 0.95 | 0.43 – 2.07 | 0.888 | 0.640
Sodium (mmol/L) | 3184 (47.0) | 2.06 | 1.17 – 3.65 | 0.013 | 0.046
Leucocytes (10⁹/L) | 3784 (55.8) | 0.98 | 0.92 – 1.04 | 0.475 | 0.91 (0.69 – 1.19)
CKD-EPI (ml/min/1.73 m²) | 3062 (45.1) | 2.70 | 1.26 – 5.80 | 0.001 | 2.70 (1.26 – 5.80)
Oxygen saturation (%) | 6322 (93.2) | NA | | | 0.001
Positive microbiological blood culture | 0 (0) | NA | | | 0.001
Number of biochemical tests (≥20 versus <20) | 0 (0) | 3.63 | 2.45 – 5.37 | <0.0001 | 3.63 (2.45 – 5.37)

**Multivariate analysis**

The significant variables (p<0.05) were identified from the univariate analysis and taken forward to the next stage.

In all 20 imputed datasets, both backward and forward elimination procedure in multivariate analysis identified the same 5 variables that were significantly associated with the risk of developing a clinically relevant adverse drug event. It appeared that these 5 predictor variables did not have missing values. Therefore, the final analysis could be performed with the original, complete dataset.

The coefficients (β), standard errors (SE) and odds ratios (OR) with 95% confidence intervals of the variables are shown in Table 3. The final model comprised age, number of biochemical tests ordered, heparin/LMWH in therapeutic dose, use of opioids and use of cardiovascular drugs at the time of hospital admission.

**Figure 1. The ROC curve of the model**

The AUC of the model was 0.858 (95% CI 0.831-0.884). The ROC curve is shown in Figure 1. The validation of the model using bootstrap samples showed an over-optimism of 0.008 and a shrinkage factor of 0.960, leading to a corrected performance of the model of 0.85 (Table 3).
When the cut-off point for a high risk of developing an ADE was set at 1.6%, the model showed a sensitivity of 80.4% and a specificity of 73.4%. At this cut-off level, positive and negative predictive value were 4.3% and 99.6%, respectively.

The formula of the logistic regression model that allows for calculating the individual risk of a clinically relevant adverse drug event to a surgical patient is shown below.

Formula individual risk = 1/(1 + exp(-1*LP))

Where LP is the so-called Linear Predictor which for our model is defined as:

Linear Predictor = 10.082 + 0.060 * age (in years) + 0.770 (in case number of biochemical tests ordered ≥ 20) + 0.604 (in case the patient uses heparin/LMWH in therapeutic dose) + 1.261 (in case the patient uses cardiovascular drugs) + 0.785 (in case the patient uses opioids)

**Discussion**

The risk prediction model resulting from this study helps to identify surgical patients that are at increased risk of sustaining a clinically relevant potentially preventable adverse drug event. This model uses five clinical variables that can be obtained routinely on hospital admission, and that can be incorporated into clinical practice as a tool to target patients that can benefit from interventions aimed at reducing potentially preventable clinically relevant drug related problems during hospital stay at surgical wards.

The model was developed using data from the pre-intervention phase of the P-REVIEW study, that assessed clinically relevant, potentially preventable ADE among patients at surgical wards (10). This is the first study that developed a risk prediction model focusing on clinically relevant potentially preventable ADE instead of adverse drug reactions in general. This study only targeted surgical patients, which leads to a better model performance. We only included variables that are available on the first day after hospital admission to be able to operationalize a model to predict risk during hospital stay, immediately after hospital admission. Therefore, variables such as length of hospital stay, interdisciplinary consultation or admission to the intensive care during hospital stay, were not included in our analysis.

Our final model contains five variables: age of the patient, number of biochemical tests ordered, treatment with heparin/LMWH in therapeutic dose, treatment with opioids and treatment with cardiovascular drugs. Our model shows acceptable goodness of fit and discrimination performance. We can use the model not only to label patients at risk to experience a drug-related event but also to label patients that are very unlikely to experience an event. The negative predictive value of our model is very high. Therefore, one could use this model also to identify patients for whom automated computerized clinical decision support without surveillance by the hospital pharmacist is sufficient.

An overview of studies of development and validation of risk prediction models for ADR or ADE is shown in Table 4. Other studies showed different predicting variables and found an area under the receiver operator characteristic curve (AUROC), varying between 0.70-0.74, with relatively low sensitivity and specificity scores. We hypothesized that focusing on patient cohorts with restricted clinical characteristics (surgical patients) and focusing on clinically relevant, potentially preventable adverse drug events, instead of adverse drug reactions in general would lead to a better performing prediction model.

In our study, the strongest independent risk factor was the age of the patients. Well known from many other studies, advancing age is associated with an increased number of comorbidities in association with polypharmacy resulting in an increased risk of ADEs (2, 3, 13).

This is the first study that explores the number of biochemical tests ordered as a predictive factor for drug related events. We hypothesized that besides the use of specific laboratory values as electronic triggers, the number of biochemical tests might also be useful to identify a risk of ADE during hospital admission. Before diagnosing the patient’s condition, the physician may have an uneasy feeling which makes him concerned about a possible adverse outcome. This suspicion alerts the physician and leads to increased laboratory orders to clarify the patient’s condition and to prevent serious problems. Moreover, deviant laboratory values will lead to further monitoring (22). Consequently, the number of biochemical tests might be a useful electronic trigger to identify a patient at risk for ADE (16, 23). In our study this factor has shown to be a strong predictor for drug related problems at surgical wards.

Surgery in patients who use anticoagulation therapy, is a challenge. Guidelines on perioperative management of anticoagulation are complicated and people are at risk of either bleeding or thrombosis because of the surgical procedures. For patients with a high risk of thromboembolism, measured with a CHA2DS2-VASC score, needing certain surgical procedures, it is necessary to perform bridging with LMWH at therapeutic dose during the perioperative period. If this procedure is not correctly performed, these patients are at high risk of serious ADEs. Pardo Carbello et al. already described that the most frequent cause of fatal ADE is haemorrhage (24).

We found that use of cardiovascular drugs and use of opioids are important risk factors in surgical patients. Cardiovascular drugs are generally used by a vulnerable older population with multiple co-morbidities. Use of opioids often points out (temporary) severe morbidity. It is already known from literature that patients that use these drugs have an increased risk of experiencing ADEs (15, 25).

This study has several strengths. The P-REVIEW database contains information on clinically relevant potentially preventable drug related events (leading to death, temporary or permanent disability, increases hospital stay or readmission) in a very large cohort. Aiming at prevention of patient harm, it seems more rational to focus on clinically relevant, potentially preventable adverse events, instead of adverse reactions in general. We focused on patients on surgical wards. By studying patient cohorts with restricted clinical characteristics the performance of risk prediction models will improve. Furthermore, we used variables that can be obtained routinely on hospital admission, so implementation
Table 4. Overview studies of development and validation of risk prediction models for ADR or ADE

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Setting and country</th>
<th>Sample size and population</th>
<th>Outcome</th>
<th>Predicting variables in the model</th>
<th>Model performance</th>
<th>Model validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>McElnay et al. (1997)(7)</td>
<td>General hospital, United Kingdom</td>
<td>929 patients (&gt; 65 years old)</td>
<td>ADE</td>
<td>Digoxine - Antidepressants - Gastrointestinal disorders - Chronic obstructive airways disease - Angina - Abnormal potassium level - Thinks drugs are responsible for hospital admission</td>
<td>AUROC not presented</td>
<td>204 patients Sensitivity 41% Specificity 69%</td>
</tr>
<tr>
<td>Trivalle et al. (2011)(9)</td>
<td>Geriatric rehabilitation centers, France</td>
<td>526 patients</td>
<td>ADE</td>
<td>Number of medications - Antipsychotic treatment - Recent anticoagulant use</td>
<td>AUROC: 0.70</td>
<td>Bootstrapping</td>
</tr>
<tr>
<td>Tangisuran et al. (2014)(8)</td>
<td>Teaching hospital, United Kingdom</td>
<td>690 patients (&gt;65 years old)</td>
<td>ADR</td>
<td>Hypertension - Number of medications &gt; 8 - Length of stay &gt; 12 days - Antidepressants - Elevated white cell count</td>
<td>AUROC: 0.74</td>
<td>Sensitivity 60% Specificity 55%</td>
</tr>
<tr>
<td>Onder et al. (2010)(4)</td>
<td>Community and university-based hospitals, Italy</td>
<td>5936 elderly patients</td>
<td>ADR</td>
<td>Number of medications - History of ADR - Heart failure - Liver disease - Presence of 4 or more comorbidities - Renal failure</td>
<td>AUROC: 0.71</td>
<td>Sensitivity 68% Specificity 65%</td>
</tr>
<tr>
<td>The present study</td>
<td>Teaching hospitals, the Netherlands</td>
<td>6780 admissions of 5940 surgical patients</td>
<td>Clinically relevant, potentially preventable ADE</td>
<td>Age - Number of biochemical tests ordered - Heparin/LMWH in therapeutic dose - Cardiovascular drugs - Opioids</td>
<td>AUROC: 0.86</td>
<td>Sensitivity 80% Specificity 75%</td>
</tr>
</tbody>
</table>

Abbreviations: ADE: adverse drug event; ADR: adverse drug reaction; AUROC: Area under the Receiver Operator Characteristic Curve; LMWH: low molecular weight heparin.

Conclusions

A risk prediction model was developed to identify surgical patients at risk of experiencing a clinically relevant, potentially preventable adverse drug event during hospital admission. The resulting model contains five variables: age of the patient, number of biochemical tests ordered, treatment with heparin/LMWH in therapeutic dose, treatment with opioids, and treatment with cardiovascular drugs. This model can be used to guide the hospital pharmacist to downstage interventions and to improve medication safety.

The development of our risk prediction model has potentially important implications for clinical practice. By using this model, lower-risk patients could be managed less extensively (for instance, only using automated CPOE/CDSS), whereas higher risk patients could receive more intensive interventions, such as medication review, aimed at reducing drug-related adverse outcomes. Such selective use of interventions could help to improve the cost-effectiveness of medication safety interventions. In that way, this risk model, that combines clinical and medication-related variables can guide clinical intervention, delivered as part of an integrated system built around the principles of medication safety.

Our risk model can be incorporated into a CPOE system and thereby generate automatic risk evaluation based on patient data and hospital data. By using our model, the hospital pharmacist can manage interventions, help to prevent medication errors, and thereby contribute to improving medication safety.

In our analysis, we used potentially predictive variables that were available in the P-REVIEW database. Mostly, these data were automatically obtained from hospital databases. The lack of automated coded information for some variables limited the use of these variables, e.g. information on co-morbidities using the International Classification of Diseases (ICD-10), frailty or cognitive impairment, reason for hospital admission or type of performed surgery. We internally validated our model by bootstrapping but we have not yet been able to externally validate our model by clinical practice.
References

Chapter 6

The effects of substitution of hospital ward care from medical doctors to physician assistants on non-adherence to guidelines on medication prescribing

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Arno Kalkman
Patricia van den Bemt
Peter De Smet
Michel Wensing
Kees Kramers
Miranda Laurant

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Abstract

Aim
This study determined the effect of substitution of inpatient care from medical doctors (MDs) to physician assistants (PAs) on non-adherence to guidelines on medication prescribing.

Methods
A multicenter matched-controlled study was performed comparing wards on which PAs provide medical care in collaboration with MDs (PA/MD model), with wards on which only MDs provide medical care (MD model). A set of 17 quality indicators to measure non-adherence to guidelines on medication prescribing by PAs and MDs was composed by 14 experts in a modified Delphi procedure. The indicators concerned different pharmacotherapeutic subjects, such as gastric protection in case of use of NSAID or prevention of obstipation in case of use of opioids. These indicators were expressed in proportions by dividing the number of patients in which the prescriber did not adhere to a guideline, by all patients that were applicable. Multivariable regression analysis was performed in order to adjust for potential confounders.

Results
1021 patients from 17 hospital wards in the ‘PA/MD model’ group and 1286 patients from 17 hospital wards in the ‘MD model’ group were included. Two of the 17 quality indicators showed significantly less non-adherence to guidelines for the PA/MD model; the indicators concerning prescribing gastric protection in case of use of NSAID in combination with corticosteroids (OR 0.42, 95% CI 0.19-0.90) and in case of use of NSAID in patients older than 70 years (OR 0.47, 95% CI 0.23-0.95). For none of the other quality indicators showed significantly less non-adherence to guidelines for the PA/MD model; the indicators concerning prescribing gastric protection in case of use of NSAID in combination with corticosteroids (OR 0.42, 95% CI 0.19-0.90) and in case of use of NSAID in patients older than 70 years (OR 0.47, 95% CI 0.23-0.95). For none of the other quality indicators for prescribing of medication a difference between the MD model and the PA/MD model was found.

Conclusion
This study suggests that the non-adherence to guidelines on medication prescribing on wards with the PA/MD model does not differ from wards with traditional house staffing by MDs only. Further research is needed to determine quality, efficiency and safety of prescribing behavior of PAs.

Introduction
Hospital care, nowadays, is characterized by a rising prevalence of chronic diseases, ongoing specialization in medical disciplines and increasing dependence on new technologies (1). To cope with these challenges, many hospitals in different countries have introduced dedicated ward physicians, who are responsible for the delivery and coordination of the daily medical care of hospitalized patients. Their work includes daily ward rounds, performing physical examinations, making decisions regarding necessary tests, treatments and procedures, rendering medical diagnoses and generating and reviewing clinical data (2). The role of this ward physician has mainly been fulfilled by medical residents or medical specialists (2, 3). The turnover of these ward physicians is traditionally high due to use of recent medical graduates who continue on to do fellowships and the mandatory rotational cycles. In recent years, however, there is an increasing pressure to deliver health care efficiently. Medical procedures are more and more standardized and there are concerns about the continuity, quality and safety of clinical processes. Therefore, these tasks are now increasingly allocated to physician assistants (PAs) in several countries, among which are the USA, Canada, the UK and the Netherlands. PAs generally do not rotate and constitute a factor of stability in the continually changing medical workforce (4-6).

A PA is a non-physician health care professional licensed to practice medicine in defined domains, in collaboration with MDs but with a substantial degree of professional autonomy (7). PAs who are employed for medical care for admitted patients usually work in a team comprising both PAs and MDs (i.e. residents, staff physicians or hospitalists). The level of professional autonomy of PAs differs between countries. The scope of practice is determined by law as well as by the competencies of the PAs, the comfort level of the MD with the PA, and the perceived needs in health care delivery. Although there is a worldwide trend of an increase of PAs in the management of hospitalized patients, scientific evidence on the impact of PAs on health care outcomes, quality and safety of care, and costs is limited. Although evidence is scarce, some studies suggest that quality and efficiency of care provided by PAs is similar to that of MDs (8-14).

Prescribing medication is considered a fundamental part of medical ward care practice. Up to 20-50% of admitted patients experience one or more adverse drug events (ADEs) during their hospital stay. Approximately 50% of these ADEs is potentially preventable. They mainly derive from prescribing errors that lead to potentially preventable morbidity, mortality and costs (15-18). Research on prescribing errors is mainly focused on prescription of medication by physicians (15-18).

Since January 2012, legislation in Dutch healthcare authorizes PAs to prescribe medication without supervision of a MD (19, 20). Evaluation of this newly acquired authority in 2015 showed that the measure had led to legalization of reserved medical procedures, already performed by PAs. It has created a perspective for PAs to further develop their profession in daily practice (20). However, scientific evidence on the quality of drug prescribing or adherence to clinical practice guidelines by PAs is hardly available. Published research about quality of drug prescribing by nurses and nurse practitioners (NPs) suggests that this is overall safe. This conclusion should however be interpreted cautiously given the methodological weaknesses in the body of research (19). Furthermore, the scope of
The effects of substitution of hospital ward care on medication prescribing

Study aim
The aim of this study was to compare the non-adherence to guidelines on medication prescribing on hospital wards where PAs fulfill the role of ward physician, in collaboration with MDs, to the wards where the role of ward physician is solely fulfilled by MDs.

Methods
Study design and setting
This study was conducted as part of a multicenter matched-controlled study comparing wards utilizing a mixed 'PA/MD model', on which PAs provide medical care in collaboration with MDs, with wards utilizing a 'MD model', on which only MDs provide medical care. This study has been described in detail previously (22).

In short, the study aimed to measure the effects of substitution of inpatient care from MDs to PAs on length of hospital stay, several indicators for quality and safety of inpatient care and patient experiences. 17 wards of the MD model were matched with 17 wards of the PA/MD model based on medical specialty and hospital type (i.e. academic versus non-academic).

Hospital wards were assigned to the PA/MD group if PAs were employed at the wards as substitutes for residents or medical specialists, taking care of inpatient management and daily clinical care. The PAs had to cover at least 51% of the available ward care hours per week during dayshifts (8 a.m. till 18 p.m.) on weekdays and had to have completed a master’s PA degree. The PAs as well as the residents were supervised by attending medical specialists.

Wards were assigned to the control group if medical care was exclusively provided by MDs. Most of the MDs were residents. The resident is physically present at the department for at least a few hours each weekday, and is the first point of access to medical care. They are supervised by attending medical specialists. In some smaller hospitals, the medical specialists provide all medical care for the admitted patients.

In all hospitals in the Netherlands a computerized physician order entry (CPOE) system is implemented to support prescribing. Hospital pharmacists check medication of all patients on a daily basis with the aid of computer-generated alerts based on a national database ('G-standard; www.z-index.nl') and with clinical decision support (CDS) systems combining clinical patient data (like renal function and electrolyte levels) with the medication to assess. If necessary, hospital pharmacists warn the prescriber for specific prescribing errors.

Outcome measures
A set of quality indicators based on pharmacotherapeutic guidelines was composed to measure the quality of prescribing by PAs and MDs.

A set of 17 indicators was composed by means of a consensus procedure. First, provisional indicators were selected from scientific literature by a hospital pharmacist (JB) and an internist-clinical pharmacist (CK). The selected quality indicators had to relate to medication that has shown to frequently be involved in potentially preventable, clinically relevant, drug-related problems (15–17, 23, 24). The indicators should be clearly referenced in a national clinical practice guideline or in the SmPC (Summary of Product Characteristics) of the concerned drug. The indicators were assumed to be part of general knowledge of the prescriber, and the prescriber should be able to perform on these indicators aided by implemented hospital guidelines. Selection was also based on potential relevance for a diversity of medical specialties and available data from the matched-controlled study.

Second, an expert panel of five hospital pharmacists and nine medical specialists (two internist-clinical pharmacologists, one geriatrician-clinical pharmacologist, one nephrologist-clinical pharmacologist, one surgeon and four internists) were approached to participate in a modified Delphi procedure (25). We asked the expert panel to score the list of provisional indicators on their relevance to determine the quality of drug prescription by physicians on the ward. Scoring was done independently by e-mail. A nine-point Likert scale ranging from 1 (hardly relevant) to 9 (extremely relevant) was used to rate the indicators and also a category ‘could not assess’ was available. In addition, we asked for suggestions for new indicators. In case the suggestions for new indicators were measurable, we included the indicator in a second consensus round. We used a rating scale based on the RAND appropriateness method (26). Indicators with a median score of at least seven were considered as face valid and relevant and were selected for the final set of indicators. However, in case of too much diversity in scores for one indicator (i.e. at least 30% of the scores as well in the lowest tertile as in the highest tertile), the indicator was not selected (27). In table 1 we present the final set of 17 included quality indicators for prescribing. The indicators covered different pharmacotherapeutic subjects, such as gastric protection in case of use of NSAID or salicylates, prevention of obstipation in case of use of opioids, adequate prescribing in case of impaired renal function, adjustment of medication in case of use of iodinated radiocontrast agents, prevention of toxicity of methotrexate and avoidance of certain medication in combination with vitamin K antagonists.

The outcome measure of this study is the non-adherence to guidelines on medication prescribing measured by 17 quality indicators. These indicators are expressed in proportions by dividing the number of patients in which the prescriber did not adhere to a guideline, by all patients that were applicable. The MD model served as the reference category.
### Table 1. Indicators to measure adherence to guidelines on medication prescribing

<table>
<thead>
<tr>
<th>Quality indicator</th>
<th>Reference indicator</th>
<th>Median score by expertsa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric protection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Check whether a proton pump inhibitor was added in all patients with an ulcer in history and use of an NSAID.</td>
<td>NSAID use and prevention of gastric damage (guideline 2003 CBO)(28)</td>
<td>9</td>
</tr>
<tr>
<td>2. Check whether a proton pump inhibitor was added in all patients with an age of older than 70 years and use of an NSAID.</td>
<td>NSAID use and prevention of gastric damage (guideline 2003 CBO)(28)</td>
<td>8</td>
</tr>
<tr>
<td>3. Check whether a proton pump inhibitor was added in all patients with use of coumarines in combination with an NSAID.</td>
<td>NSAID use and prevention of gastric damage (guideline 2003 CBO)(28)</td>
<td>9</td>
</tr>
<tr>
<td>4. Check whether a proton pump inhibitor was added in all patients with use of corticosteroids in combination with an NSAID.</td>
<td>NSAID use and prevention of gastric damage (guideline 2003 CBO)(28)</td>
<td>7.5</td>
</tr>
<tr>
<td>5. Check whether a proton pump inhibitor was added in all patients with an age of older than 80 years and use of salicylates.</td>
<td>Recommendations of the Dutch NARM-Wrestling Task Force (29)</td>
<td>8</td>
</tr>
<tr>
<td><strong>Prevention of obstipation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. All patients with use of an opioid were checked whether a laxative was added. Patients with intestinal stoma were excluded.</td>
<td>Pain (guideline NHG)(30) Diagnostics and treatment of pain (31)</td>
<td>8</td>
</tr>
<tr>
<td><strong>Impaired renal function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. All patients with impaired renal function (MDRD&lt;30 ml/min/1.73m2) were checked whether an NSAID was avoided.</td>
<td>Dutch national G-standard; SmPC NSAID (32, 33)</td>
<td>9</td>
</tr>
<tr>
<td>8. All patients with impaired renal function (MDRD&lt;30 ml/min/1.73m2) were checked whether nitrofurantion was avoided.</td>
<td>Dutch national G-standard; SmPC nitrofurantion (32, 33)</td>
<td>7.5</td>
</tr>
<tr>
<td>9. All patients with impaired renal function (MDRD&lt;30 ml/min/1.73m2) were checked whether dabigatran was avoided.</td>
<td>Dutch national G-standard; SmPC dabigatran (32, 33)</td>
<td>8</td>
</tr>
<tr>
<td>10. All patients with impaired renal function (MDRD&lt;30 ml/min/1.73m2) were checked whether metformin was avoided.</td>
<td>Dutch national G-standard; SmPC metformin(32, 33)</td>
<td>8</td>
</tr>
<tr>
<td><strong>Dose adjustment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. All patients with impaired renal function and use of a therapeutic dose of LMWH were checked whether the therapeutic dose of LMWH was adjusted.</td>
<td>Dutch national G-standard; SmPC LMWH (32, 33)</td>
<td>8</td>
</tr>
<tr>
<td><strong>Use of iodinated radiocontrast</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. All patients, that received iodinated radiocontrast because of imaging diagnostic examination and use of diuretics, were checked whether the diuretic was discontinued on the day of the test.</td>
<td>Precautions for use of iodinated radiocontrast (guideline 2007 NVRI)(34)</td>
<td>7</td>
</tr>
<tr>
<td>13. All patients, that received iodinated radiocontrast because of imaging diagnostic examination and use of an NSAID, were checked whether the NSAID was discontinued on the day of the test.</td>
<td>Precautions for use of iodinated radiocontrast (guideline 2007 NVRI)(34)</td>
<td>8</td>
</tr>
</tbody>
</table>

*a*: median score of an expert panel on a nine-point scale (rated 1 to 9), performed to assess the relevance of the indicator in determining the adherence to guidelines on medication prescribing.

Abbreviations: FNT= Federation of Dutch Anticoagulant Services, NSAID = Non steroidal anti-inflammatory drug, MDRD = modification of diet in renal disease, LMWH = Low molecular weight heparin, NHG= Dutch Society of General Practitioners, NVR=Dutch Association of Radiology, PCP=pneumocystis jiroveci pneumonia

### Data collection

All required data for the quality indicators were retrospectively derived from patient medical records by trained medical students and researchers. To ensure validity, a random sample of 10% of the patient records per ward was analyzed by a second researcher, who was blinded for the outcome of the initial researcher. In case of an inter-rater agreement of less than 95%, the records of the total sample were reassessed.

### Sample size and data analysis

The sample size was calculated to detect a relative difference of 20% in length of stay (LOS), which is the primary outcome measure of the multicenter study. 34 Wards (17 in each arm) with 100 patients each were calculated to be required (22, 37). For the present study, no sample size calculation was performed.

Baseline characteristics of the study population are presented as mean and standard deviations (mean ± SD) for continuous variables, and proportion (%) for categorical variables. Quality indicators were expressed as proportions by dividing the number of patients in whom the prescriber did not adhere to a guideline, by the number of patients to which the guideline applied. To compare differences on the selected indicators between the PA/MD model and the MD model, logistic regression analyses were performed. Multivariable models were constructed to correct for relevant differences between the groups at baseline. Associations were expressed as odds ratios with 95% confidence interval. In all analyses, two-tailed p-values of 0.05 or lower were considered statistically significant. Analyses were performed with SPSS statistics version 24 (IBM Software, USA).
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Ethical considerations

Ethical approval was sought from the Research Ethics Committee of the Radboud University Nijmegen Medical Centre (registration number: 2012/306); the committee judged that ethical approval was not required under Dutch National Law. All data were handled strictly confidential and written informed consent was obtained from all patients.

Results

1021 Patients from 17 hospital wards were included in the ‘PA/MD model’ and 1286 patients from 17 hospital wards were included in the ‘MD model’. The main characteristics of the patients are summarized in table 2. Most characteristics were well balanced between the groups. Less patients in the PA/MD model group were admitted electively in comparison with the MD model (41% versus 56%).

Table 2. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>PA/MD model (n=1021)</th>
<th>MD model (n=1286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical specialty (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Surgery</td>
<td>601 (59%)</td>
<td>696 (54%)</td>
</tr>
<tr>
<td>- Gastroenterology</td>
<td>102 (10%)</td>
<td>181 (14%)</td>
</tr>
<tr>
<td>- Pulmonology</td>
<td>91 (9%)</td>
<td>107 (8%)</td>
</tr>
<tr>
<td>- Cardiology</td>
<td>101 (10%)</td>
<td>124 (10%)</td>
</tr>
<tr>
<td>- Orthopaedics</td>
<td>103 (10%)</td>
<td>100 (8%)</td>
</tr>
<tr>
<td>- ENT, head and neck oncology surgery</td>
<td>23 (2%)</td>
<td>78 (6%)</td>
</tr>
<tr>
<td>Hospital type (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Teaching</td>
<td>552 (54%)</td>
<td>709 (55%)</td>
</tr>
<tr>
<td>- Academic</td>
<td>23 (2%)</td>
<td>78 (6%)</td>
</tr>
<tr>
<td>- Non-academic</td>
<td>529 (52%)</td>
<td>631 (49%)</td>
</tr>
<tr>
<td>- Non-teaching</td>
<td>469 (46%)</td>
<td>577 (45%)</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>524 (53%)</td>
<td>682 (54%)</td>
</tr>
<tr>
<td>Age, years mean ± SD</td>
<td>64 ± 16</td>
<td>63 ± 15</td>
</tr>
<tr>
<td>Primary diagnoses (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Digestive system</td>
<td>204 (20%)</td>
<td>247 (19%)</td>
</tr>
<tr>
<td>- Circulatory system</td>
<td>158 (16%)</td>
<td>274 (22%)</td>
</tr>
<tr>
<td>- Neoplasms</td>
<td>108 (11%)</td>
<td>195 (15%)</td>
</tr>
<tr>
<td>- Musculoskeletal system and connective tissue</td>
<td>120 (12%)</td>
<td>119 (9%)</td>
</tr>
<tr>
<td>- Injury and poisoning</td>
<td>135 (13%)</td>
<td>80 (6%)</td>
</tr>
<tr>
<td>- Infectious diseases</td>
<td>59 (6%)</td>
<td>81 (6%)</td>
</tr>
<tr>
<td>- Respiratory system</td>
<td>51 (5%)</td>
<td>75 (6%)</td>
</tr>
<tr>
<td>Charlson index for co-morbidity score mean ± SD (% with score ≥1)</td>
<td>1.1 ± 1.8 (43%)</td>
<td>1.1 ± 1.8 (44%)</td>
</tr>
<tr>
<td>Type of admission (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Elective</td>
<td>402 (41%)</td>
<td>687 (56%)</td>
</tr>
<tr>
<td>- Acute</td>
<td>586 (59%)</td>
<td>547 (44%)</td>
</tr>
</tbody>
</table>

Note: Numbers may not add up to the total because of missing values

Table 3 shows the results of the quality indicators expressed as the proportion of patients in which the prescriber in the ‘PA/MD model’ group and in the ‘MD model’ group did not adhere to a pharmacotherapeutic guideline and the matching odds ratios with 95% confidence interval.

Two of the 17 quality indicators showed significantly less non-adherence for the PA/MD model. These were the indicators concerning prescribing gastric protection in case of use of NSAID in combination with corticosteroids (OR 0.42, 95% CI 0.19-0.90) and in case of use of NSAID in patients older than 70 years.

In none of the other quality indicators for non-adherence to guidelines on medication prescribing a difference between the MD model and the PA/MD mixed model was found.

Table 3. Non-adherence to pharmacotherapeutic guidelines, based on the selected quality indicators

<table>
<thead>
<tr>
<th>Quality indicator</th>
<th>PA/MD model **</th>
<th>MD model**</th>
<th>Adjusted Odds ratio *</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric protection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. All patients with an ulcer in history and use of an NSAID were checked whether a proton pump inhibitor was added.</td>
<td>0/6 (0%)</td>
<td>1/11 (9.1%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>2. All patients with an age of older than 70 years and use of an NSAID were checked whether a proton pump inhibitor was added.</td>
<td>18/113 (15.9%)</td>
<td>25/100 (25%)</td>
<td>0.47</td>
<td>0.23-0.95 (p=0.037)</td>
</tr>
<tr>
<td>3. All patients with use of coumarines in combination with an NSAID were checked whether a proton pump inhibitor was added.</td>
<td>6/27 (22.2%)</td>
<td>6/21 (28.6%)</td>
<td>0.66</td>
<td>0.18-2.48</td>
</tr>
<tr>
<td>4. All patients with use of corticosteroids in combination with an NSAID were checked whether a proton pump inhibitor was added.</td>
<td>9/58 (15.5%)</td>
<td>81/248 (32.7%)</td>
<td>0.42</td>
<td>0.19-0.90 (p=0.012)</td>
</tr>
<tr>
<td>5. All patients with an age of older than 70 years and use of salicylates were checked whether a proton pump inhibitor was added.</td>
<td>13/51 (25.5%)</td>
<td>11/50 (22%)</td>
<td>1.41</td>
<td>0.53-3.74</td>
</tr>
<tr>
<td>Prevention of obstipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. All patients with use of an opioid were checked whether a laxative was added. Patients with intestinal stoma were excluded.</td>
<td>463/606 (76.4%)</td>
<td>590/785 (75.2%)</td>
<td>1.13</td>
<td>0.87-1.46</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. All patients with impaired renal function (MDRD=30 ml/min/1.73m2) checked whether an NSAID was avoided.</td>
<td>3/24 (12.5%)</td>
<td>0/22 (0%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>8. All patients with impaired renal function (MDRD=30 ml/min/1.73m2) were checked whether nitrofurantoin was avoided.</td>
<td>1/24 (4.2%)</td>
<td>2/22 (9.1%)</td>
<td>0.41</td>
<td>0.03-4.96</td>
</tr>
<tr>
<td>9. All patients with impaired renal function (MDRD=30 ml/min/1.73m2) were checked whether dabigatran was avoided.</td>
<td>0/24 (0%)</td>
<td>1/22 (4.5%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>10. All patients with impaired renal function (MDRD=30 ml/min/1.73m2) whether checked if metformin was avoided.</td>
<td>7/24 (29.2%)</td>
<td>3/22 (13.6%)</td>
<td>2.58</td>
<td>0.57-11.62</td>
</tr>
</tbody>
</table>
The effects of substitution of hospital ward care on medication prescribing

In recent years the PA has been increasingly introduced in the hospital. A PA is a non-physician health care professional licensed to practice medicine in defined domains and trained to do tasks that were formerly performed by physicians only. The primary motive for employing a PA in Dutch health care is to increase continuity and quality of care (38). The level of professional autonomy of PAs differs between countries. From the introduction of the PA there has been debate about prescribing by PAs(20). It has been suggested that only physicians have the capability to prescribe medication and that only physicians should be allowed to do so. Prescribing is viewed as a very complex, risky clinical task. Many studies have shown that prescription errors made by physicians lead to preventable adverse events in hospitals (15-18). Nowadays, although with different levels of autonomy, in most countries PAs have been authorized to prescribe a limited list of medication, based on the specific training of the PA. Until now, there have been no studies to evaluate prescribing of PAs compared to MDs.

It has been shown that continuity of care is higher on wards with PAs, and that PAs often have more years of experience on the ward than residents do. As a consequence, PAs might be more familiar with prevailing clinical practice protocols and pharmacotherapeutic guidelines (39). This could implicate that PAs are more capable, dedicated and motivated to follow guidelines. On the other hand, because of a lower degree of autonomy of the PA, it may also be more difficult for a PA to deviate from guidelines, when this is needed in certain circumstances. We found that the PA/MD model performed better on the quality indicators concerning gastric protection in case of NSAID use in combination with another risk factor. Van den Bemt et al. found that the proportion of admissions in which MDs were not compliant with guidelines on gastric protection in case of use of NSAID in hospitalized surgical patients was 46.6%(40). In our study we found a better performance in both models, but a significant better result in case of the PA/MD model. For this specific guideline, this could confirm the hypothesis that PAs are more dedicated to follow the guideline. For the indicator that measures prevention of obstipation in case of use of opioids we found no difference and also a poor adherence to the guideline (non-adherence 76.4% for the PA/MD model and 75.2% for the MD model). We excluded patients with intestinal stoma, but for this guideline there are more situations in daily practice in which a prescriber could deviate intentionally from this guideline. It is possible that better compliance by PAs is masked by a higher percentage of just deviation from guidelines by MDs because of certain patient circumstances. Detailed clinical data necessary to assess justified deviation of the guideline was not available in this study.

We found that a diuretic, NSAID, or metformin in case of renal failure, was often not justified deviation of the guideline was not available in this study.

Discussion

In this study we aimed to determine the effect of substitution of inpatient care from MDs to PAs on non-adherence to guidelines on medication prescribing on the ward. Indicators of prescribing gastric protection in case of use of NSAID by patients with an age over 70 years or in combination with use of corticosteroids showed less non-adherence in the 'PA/MD model' group than in 'MD model' group. None of the other quality indicators showed a significant association between the involvement of PAs and the quality of prescribing. Adherence to recommendations varied across indicators, but tended to be low overall. Although we have to interpret the results cautiously because of the relatively small sample size for several quality indicators, this study suggests that the non-adherence to guidelines on medication prescribing on wards on which PAs provide medical care in collaboration with MDs (PA/MD model), does not differ from wards on which only MDs provide medical care (MD model).

### Quality indicator | PA/MD model | MD model | Adjusted Odds ratio
--- | --- | --- | ---
1. All patients with impaired renal function and use of a therapeutic dose of LMWH were checked whether the therapeutic dose of LMWH was adjusted | 0/2 (0%) | 0/5 (0%) | NA
Use of iodinated radiocontrast | 12. All patients, that received iodinated radiocontrast because of imaging diagnostic examination and use of diuretics, were checked whether the diuretic was discontinued on the day of the test | 48/67 (71.6%) | 51/68 (75%) | 0.80 0.36-1.78
13. All patients, that received iodinated radiocontrast because of imaging diagnostic examination and use of NSAID, were checked whether the NSAID was discontinued on the day of the test | 44/70 (62.9%) | 37/60 (61.7%) | 1.02 0.49-2.12
14. All patients, that received iodinated radiocontrast because of imaging diagnostic examination and a MD/ID<60 ml/min/1.73m2, were checked whether the metformin was discontinued on the day of the test. | 2/2 (100%) | 4/9 (44.4%) | NA
Prevention of toxicity | 15. All patients, that used methotrexate, were checked on concurrent use of folic acid. | 0/8 (0%) | 0/12 (0%) | NA
Dosing of vitamin K antagonists | 16. All patients with use of vitamin K antagonist were checked whether miconazole was avoided. | 1/124 (0.8%) | 1/153 (0.7%) | 1.28 0.08-20.71
17. All patients with use of vitamin K antagonist were checked whether cotrimoxazol was avoided. Only for patients with PJP this combination was allowed. | 4/124 (3.2%) | 0/153 (0%) | NA

NA=not applicable because of limited number of cases
* Adjusted for type of admission (elective or acute)
** Quality indicators are expressed in proportions by dividing the number of patients in which the prescriber did not adhere to a guideline, by all patients that were applicable. The MD model served as the reference category.
but they did not measure discontinuation of drugs according to the guideline (41). Overall, adherence to guidelines varied across the indicators we measured, but tended to be low. This is in line with earlier research on pharmacotherapeutic guideline adherence (40-42). Different variables, such as organizational, guideline or patient factors but also health professional factors, that are associated with poor guideline adherence, have been described (43). Our study suggests that a poor guideline adherence cannot be explained by a difference in prescribing by PAs and MDs.

This study has some methodological strengths and limitations. A major strength of this study is the multicenter design. 15 wards in teaching hospitals and 19 wards in non-teaching hospitals were included. This is approximately in proportion with the general situation in the Netherlands (36 teaching hospitals and 60 nonteaching hospitals). Most of the wards were of a surgical (sub)specialty. We know that, in the Netherlands, most of the PAs are employed at a surgical department.

Another strength of the study is the broad set of indicators that measures non-adherence to guidelines and covers different pharmacotherapeutic subjects. Moreover, this set was composed by a consensus procedure in which 14 medical experts participated in a modified Delphi procedure to select a final set of representative indicators, that are considered clinically relevant for inpatient care.

One of the limitations is the non-randomized design of the study, which implies an increased risk of confounding. We took this into account by performing a multivariable analysis. However, we cannot exclude that there are small local differences like the organization of ward care (care by resident or specialist, arrangement of supervision), policies on the medication process, implementation of CPOE based clinical decision support, and patient case-mix, that are not accounted for in the multivariable analysis. Another limitation of this study is the relatively small sample size for several quality indicators we measured. The primary study was not powered to detect effects on prescribing indicators. Results of the statistical analyses should therefore be interpreted with caution.

The study compared wards with a PA/MD model to wards with traditional house staffing by MDs only. This implicates that prescribing of medication on the wards with the PA/MD model was not only performed by PAs. It is more likely that we measured a team performance than the performance of the PA alone. However, PAs covered most of the available ward care hours per week during dayshifts (68% (IQR 48-77%))(39). Moreover, measurement on the ward with several medical residents and medical specialists can also be interpreted as team performance.

It is important to obtain more evidence on quality, safety or efficiency of prescribing by PAs to be sure that the complex task of prescribing can be performed by these medically trained professionals. Dedicated research should be designed and performed with measures as guideline adherence, adverse drug events and prescribing errors, linked to relevant clinical patient outcome measures.

Conclusions
This study suggests that the non-adherence to guidelines on medication prescribing on wards with the PA/MD model does not differ from wards with traditional house staffing by MDs only. Further research is needed to determine quality, efficiency and safety of prescribing behavior of PAs.

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References


Chapter 7

Summarizing discussion
Introduction
Pharmacotherapy is the most frequently used therapeutic tool for the physician to treat patients. In addition to the beneficial effects, use of drugs also introduces risks of adverse drug events (ADE) or medication errors (ME). Drug treatment is a complex process and failures can occur in different steps of the drug therapy process (reconciling, prescribing, transcribing, dispensing, administering and monitoring), but especially prescribing is a frequent cause of ADE (1). This leads to potentially preventable morbidity, mortality and costs (2-4).

In recent years, medication use has increased and contributed to an improvement in quality of life and increase of life expectancy (5). To get an impression of the vast number of drugs used in the Netherlands, data provided by the Dutch Foundation for Pharmaceutical Statistics (SFK) and the National Healthcare Institute can be used (6, 7). In 2015 the Dutch population of 17 million used a total of 8,737 million Defined Daily Doses (DDDs) (6, 7). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (8). 3,244 million of these DDDs concern medicines within the cardiovascular risk management (7).

Many of the patients who are prescribed medication are elderly and vulnerable. They have comorbidities, suffer from cognitive and social problems and use multiple high risk drugs. According to the definition in the multidisciplinary guideline (MDR) “Polypharmacy in Elderly” from the Dutch Association of General Practitioners (NHG), a polypharmacy patient takes five or more drugs for chronic conditions (9). The number of drugs is counted on ATC3 code level. In the Anatomical Therapeutic Chemical (ATC) classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic and chemical properties (8).

In 2015 there were 1.57 million polypharmacy patients, which was 9.3% of the total number of insured persons in the Netherlands. In 2011 they counted 1.35 million patients (6).

Nearly 65% of all polypharmacy patients are 65 years of age and older. Of the patients of 75 years and older, half of the patients take five or more drugs. 65% of the polypharmacy patients use antithrombotics and a large group of polypharmacy patients receive medicines for heart failure and hypertension (6, 7). This increase in drug consumption by more complex patients has inevitably led to an increase of side effects (ADR), medication errors and adverse drug events (fig. 1.) (10).

For this reason, medication safety has become an important theme in hospitals and several interventions have been introduced to cope with these drug-related problems. The risk of accidental injury during hospitalization has remained unchanged in recent years (8% of hospital admissions in 2008 and 7.1% of hospital admissions in 2012) and potentially preventable harm decreased (2.9 % versus 1.3%). However, despite all efforts put in medication safety interventions, promoting adherence to professional standards and decreasing shortcomings in organization of care, the potentially preventable harm caused by medication in hospitals remains unchanged (11, 12).

Figure 1. Venn diagram showing the relation between adverse events, adverse drug reactions, and medication errors (10).

Patient harm caused by medication has contributed to a negative image of drugs. In the Western world the expectations of therapeutic possibilities, both pharmacological and technological, are very high. Several publications of reports that address the increase in hospital costs and patient harm due to the use of drugs have attracted a lot of media attention (3, 13). Although the title of the report “To err is human” sounds mild, there is little place for forgiveness of errors in the complex process of patient treatment. It appears that introducing recommendations, implementing clinical practice guidelines and introducing changes in the process of healthcare delivery progress slowly and require a lot of attention and energy from different healthcare providers. Working on medication safety remains a continuous process of measuring, audit and feedback followed by improving and adapting the system and care processes. This thesis describes a multifaceted approach in large teaching hospitals in the Netherlands, combining different medication safety interventions, to address the problem of prescribing errors leading to adverse drug events.

In this final chapter our main results are reviewed in a wider perspective in relation to the main objectives of this thesis. First the challenges of the methodology of intervention studies on medication safety will be addressed. After that the different components of the multifaceted intervention we studied will be discussed. This intervention includes
The major part of the data collection was performed automatically, using a validated experts. Blinded all case record forms with respect to the study period before assessment by the permanent disability, increased hospital stay or readmission) as the primary outcome. We in study design (16). We collected data on a very large patient cohort. With this large automated with special-purpose scripting, should be validated. These steps, that may be made ad hoc, codified into procedures or processing steps. These steps, that may be made ad hoc, codified into procedures or missing or misinterpreted. The automatic extraction from data from being incorrect, missing, or misinterpreted. The automatic extraction from financial resources (15). The validity of conclusions drawn in this kind of research critically expressed concerns on methods of data management, often caused by a shortage of investigator initiated clinical research 2014-2016” the Dutch Inspectorate of Healthcare (if not all) of studies lack robust data collection methods. In their report “Supervision on the risk of reporting bias through selective outcome reporting was high. The majority was influenced by other confounders during the study period (performance bias). Also, the association between drug treatment and patient harm, the degree in which the causal drug contributes to the adverse event often remains unclear. In addition to the design of the study, the design of the intervention itself needs attention. In the P-REVIEW study we chose a multifaceted approach by combining different interventions. We hypothesized that the combination of interventions would address different factors that may influence the quality of prescribing. Conscious combination of interventions leads to more efficient and effective strategies. For instance, the effect of educational programs could be boosted by frequent consultation and audit of the prescriber on the wards. Medication review would become more feasible by introducing interventions. We hypothesized that the combination of interventions would address different factors that may influence the quality of prescribing. Conscious combination of interventions leads to more efficient and effective strategies. For instance, the effect of educational programs could be boosted by frequent consultation and audit of the prescriber on the wards. Medication review would become more feasible by introducing methods of risk stratification of patients. De Smet et al. promoted a combination of implicit and explicit screening criteria in medication review as it may offer a more thorough approach (18). We also hypothesized that the support of education of the prescriber by the hospital pharmacist in a more pro-active role is more efficient and effective than the traditional reactive role of the hospital pharmacist in medication surveillance. It is better to prevent prescribing errors than to solve them.

**Components of the multifaceted intervention**

**Education of healthcare providers**

In the review (Chapter 2) we searched for studies that evaluated the effects of educational programs for hospital physicians and reported outcomes on (potential) patient harm. These studies showed a large variation in study settings and in the percentages found on intermediate outcome markers such as prescription errors and potential ADEs. Four out of seven studies in which the intervention was education alone, showed efficacy. All studies in which education was the main part of a multifaceted intervention showed education of the prescriber, implementation of guidelines, medication review and the use of information technology. This multifaceted approach must be applied in hospitals by using risk stratification in daily practice, embedded in a transparent and efficient organization of healthcare and medication safety programs. This chapter will be concluded by providing recommendations for clinical practice and future research.

**Methodology of intervention studies on medication safety**

To design studies that assess the effect of different interventions to improve medication safety is challenging. Earlier medication safety intervention studies were generally insufficiently powered to detect actual patient harm. They mostly focused on surrogate endpoints such as increase of knowledge or skills, or a decrease of prescriptions errors or medication discrepancies. In some cases, they estimated potential harm instead of measuring clinically relevant outcomes. A randomized controlled design is almost never deemed possible and many studies used non-blinded designs and lacked robust data collection methods. We describe a systematic review (Chapter 2) that gives an overview of original research papers on the effect of education of prescribers that report outcomes on (potential) patient harm (14).

We assessed the methodological quality of these studies using the Methodological Index for Non-Randomized studies (MINORS) checklist and the suggested risk of bias criteria for Effective Practice and Organization of Care (EPOC) reviews. We found important methodological limitations of the studies such as short follow-ups (less than 3 months), lack of appropriate (equivalent, contemporary) control groups and absence of blinded evaluation of the outcome. It was generally unclear whether the educational intervention was independent of other changes over time and whether the outcome measurement was influenced by other confounders during the study period (performance bias). Also, the risk of reporting bias through selective outcome reporting was high. The majority (if not all) of studies lack robust data collection methods. In their report “Supervision on investigator initiated clinical research 2014-2016” the Dutch Inspectorate of Healthcare expressed concerns on methods of data management, often caused by a shortage of financial resources (15). The validity of conclusions drawn in this kind of research critically depends on the validity of the data used. Adequate measures must be taken to prevent the data from being incorrect, missing, or misinterpreted. The automatic extraction from hospital databases and use of these data for medical research involves additional data processing steps. These steps, that may be made ad hoc, codified into procedures or automated with special-purpose scripting, should be validated.

In the design of the P-REVIEW study (Chapter 3) we tried to overcome such limitations in study design (16). We collected data on a very large patient cohort. With this large cohort it was possible to study clinically relevant outcome measures (death, temporary or permanent disability, increased hospital stay or readmission) as the primary outcome. We blinded all case record forms with respect to the study period before assessment by the experts. The major part of the data collection was performed automatically, using a validated multisource Microsoft Access database. Also the identification of possible cases with a clinically relevant, drug-related problem based on a trigger list was performed semi-automatically. The Laboratory for Quality Software (LaQuSo) connected to the University of Technology in Eindhoven validated three steps of data generation of the P-REVIEW database; automated collection of data, general data clean up, conversion and filtering steps and specific queries as additional filtering and aggregation steps (17). Detecting clinically relevant adverse drug events requires an intensive outcome-based approach, such as chart review by experts. Even when an automatic trigger instrument based on electronic patient records is used to select possible drug related problems, chart review of large patient cohorts remains time-consuming. The assessment of the causal association between drug treatment and patient harm and the preventability of the event is also challenging, since a high inter-rater variability has been described among experts. Using a standardized causality algorithm can help to achieve a reproducible assessment, but a clinical and inevitably subjective judgement will be required for an evaluation of other contributing factors such as disease and patient related factors. In the P-REVIEW study we used three expert teams consisting of a hospital pharmacist and a hospital-based physician, assessing adverse drug events from their own perspective given their profession. To minimize bias due to subjectivity of the assessment process it is important to use standardized methods and intensive sessions to agree upon adverse drug events included. Even when experts completely agree on the causal association between drug treatment and patient harm, the degree in which the causal drug contributes to the adverse event often remains unclear.

In addition to the design of the study, the design of the intervention itself needs attention. In the P-REVIEW study we chose a multifaceted approach by combining different interventions. We hypothesized that the combination of interventions would address different factors that may influence the quality of prescribing. Conscious combination of interventions leads to more efficient and effective strategies. For instance, the effect of educational programs could be boosted by frequent consultation and audit of the prescriber on the wards. Medication review would become more feasible by introducing methods of risk stratification of patients. De Smet et al. promoted a combination of implicit and explicit screening criteria in medication review as it may offer a more thorough approach (18). We also hypothesized that the support of education of the prescriber by the hospital pharmacist in a more pro-active role is more efficient and effective than the traditional reactive role of the hospital pharmacist in medication surveillance. It is better to prevent prescribing errors than to solve them.
positive results. Education alone may not have a large effect, but education embedded in a broader array of measures aimed at appropriate prescribing may be more effective. The P-REVIEW study (Chapter 3) was designed to determine whether a multifaceted intervention of educating the prescriber combined with medication review and pharmaceutical visits to the ward by the hospital pharmacist could lead to a reduction in drug-related complications among surgical patients. A total of 6780 admissions of 5940 patients to surgical patients to surgical, urological and orthopaedic wards during the usual care period and 6484 admissions of 5711 patients during the intervention period were included. A significantly lower proportion of admissions with one or more clinically relevant, potentially preventable, drug-related problems (including death, temporary or sustained disability, increased length of hospital stay or readmission within 30 days) occurred in the intervention period (1.1% (73/6484) compared to the usual care period (1.6% (106/6780)) (p=0.029). The relative risk (RR) was 0.72 (95% CI 0.53-0.97). Several types of drug-related problems occurred less frequently.

The P-REVIEW study shows that education and support of the prescribing physician with respect to high-risk patients in surgical departments leads to a significant, clinically relevant benefit for patients. However, further work is needed to develop effective educational interventions. The knowledge of how to teach effectively should be combined with optimizing the content of the education. Clearly, educational programs need a follow-up to enhance learning retention. We recently developed E-learning modules of the P-REVIEW educational programs. When these E-learning modules are followed by classroom sessions, efficiency and efficacy for students and teachers may be higher as the result of regular education sessions. The content of pharmacology education should be related to known risk factors for medication errors in hospital patients, and should focus on the use of high-risk drugs in high-risk patients or high-risk situations. Therefore, these programs need to be adjusted in time. For Dutch pre-graduate medical students a mandatory “License to prescribe” has been introduced (19). It would be useful to investigate if a mandatory test for physicians in hospitals can be introduced. If this exam has been passed, physicians will be allowed to prescribe. We suggest that educational sessions should be combined with other measures to improve medication safety. Workplace-based pharmacotherapy education, using complementary knowledge of different specialties, is effective. The P-REVIEW study showed that continuous audit and feedback on the main pharmacological issues and complementary knowledge of different specialties, is effective. The P-REVIEW study showed that these subjects are frequently involved in potentially preventable, clinically relevant, drug-related problems. Non-adherence was observed significantly less often during the intervention period as compared to the usual care period.

Not only the development, but more importantly the implementation and evaluation of guidelines needs attention in coming years. Known determinants of practices that prevent or enable guideline adherence or, more generally, adherence to healthcare process agreements should be taken into account in clear implementation projects in hospitals. These are for instance guideline factors, such as quality of evidence and accessibility of the guideline, organizational factors and resources, such as the information system, frequent rotations of physicians on the ward, workload, the presence of a continuous education system, patient factors such as increasingly complex multi-morbidity and also individual health professional factors, such as knowledge and skills, awareness and professional behaviour. By a continuous process of audit and feedback, implementation methods and adherence to guidelines of prescribers should be followed. However, it is often not necessary to pursue 100% adherence. In individual cases the physician may correctly decide to deviate from the guideline.

Medication review
Medication review by clinical pharmacists and clinical pharmacologists has been used as a tool to improve prescribing quality in hospital patients. However, the application of medication review is rather time-consuming in practice. A combination of risk stratification tools to identify patients at risk to experience drug-related problems during hospital stay and who would benefit from medication review is therefore indispensable. Also further automatization of some of the used criteria during medication review, by developing more intelligent clinical decision support, could make the efforts of the hospital pharmacist more efficient.

On the other hand, when medication review is integrated in an educational program
and considering the purpose of the medication review is not only to detect adverse drug risks but also to educate the prescriber in good prescribing and to enhance guideline adherence, it may not be needed to address all possible drug related problems. Low-risk patients (without medication reviews) may also benefit from the effect of such an intervention.

In the P-REVIEW study (Chapter 3) hospital pharmacists performed medication reviews as part of the multifaceted intervention. This systematic assessment of the medication of the patient in combination with assessment of the clinical data of the patient was performed using a standardized checklist (Appendix 2) and targeted patients at risk for potentially preventable, drug-related problems (16). We developed this checklist based on expert experience and recent literature on prescribing errors and drug-related problems (3). We also used different screening tools described in literature as input for a comprehensive assessment of the medication of the patient, such as the STOPP and START criteria (24).

Hamilton et al. showed that STOPP criteria are significantly associated with potentially preventable ADEs in older people that cause or contribute to urgent hospitalization (25). Verdoom et al. however showed recently that the majority of drug-related problems identified during medication review was not associated with STOPP/START criteria (26), and (solely) these explicit criteria may not very useful in the clinical practice of hospital care.

Hospital pharmacists were trained to perform medication safety consultations, combining a medication review and a visit to the ward to discuss potential drug related problems and associated recommendations. The development of the method of medication review and the training and experience of hospital pharmacists and clinical pharmacologist to perform reviews of good quality need great attention and it would be useful to share experiences in hospitals at a national level.

Risk prediction tools in clinical practice
Risk prediction is a routine component in daily care practice in many specific areas (e.g. approaches used to determine stroke risk in patients with atrial fibrillation). Risk stratification of potentially preventable, clinically relevant adverse drug events should be able to assist in patient prioritization, supporting clinicians and hospital pharmacists to make decisions about treatment, and can deliver more efficient healthcare service. If we are able to identify patients at risk for drug adverse events in the different wards of the hospital, we can implement all possible interventions more efficient. Risk models need an acceptable goodness of fit and good discriminative performance. A low specificity means that the model may incorrectly label patients at risk who will not develop a drug-related event. This may lead to inefficient use of resources due to interventions or increased monitoring.

We describe the results of a study in which the P-REVIEW dataset was analyzed to develop a risk-prediction model (Chapter 5) that could identify the patients at risk for potentially preventable clinically relevant drug related problems during admission at the surgical ward, at time of hospital admission (27). 6780 admissions of patients at surgical wards were included. In 102 patients a clinically relevant, potentially preventable adverse drug event during hospital stay was detected. The resulting model contained five variables including age, number of biochemical tests, heparine/LMWH in therapeutic dose, opioids and cardiovascular drugs. The AUC was 0.86 (95% CI 0.83-0.88). When the cut-off point for a high risk of developing an ADE was set to a model-predicted probability of 1.6%, the model shows a sensitivity of 80.4%, and a specificity of 73.4%. The positive predictive value is 4.5% and the negative predictive value is 99.6%. These results implicate that this model should not only be used to label hospitalized patients at risk to experience a drug-related event but especially to label patients that are unlikely to experience a drug related event. We can downgrade interventions for this group of patients and use the resources for patients with a higher risk.

A recent review identified four studies that developed adverse drug reaction (ADR) risk-prediction tools (28). These tools had poor to modest performance and did not address clinical impact or implementation, thereby limiting universal applicability. Because a large number of variables contribute to ADR occurrence in patients, it is impossible to correctly predict every ADR in every patient. To improve ADR or ADE risk prediction strategies, they should focus either on one specific harmful ADR (e.g. gastrointestinal or intracranial bleeding) or ADRs in patients with a particular illness or clinical characteristic, for instance patients with a delirium, studied by de Wit et al. (29), or surgical patients, as performed in our study. Also we believe it is more efficient to focus on clinically relevant, preventable adverse drug events instead of adverse drug reactions to develop a risk prediction tool, of which implementation actually leads to more efficient healthcare. Our study aimed to predict the risk of a surgical patient at time of hospital admission. Therefore, variables such as length of hospital stay, interdisciplinary consultation or admission to the intensive care during hospital stay, were not included in our analysis. These variables must be considered in further research to develop models that follow a possible increasing risk during hospital stay.

The performance of risk-prediction models will increase when we will be able to study more potentially predictive factors. Therefore we need more structured automated documentation of patient related factors such as comorbidities, diagnoses, reason for hospital admission, type of surgery, cognitive impairment and frailty, organizational factors or drug-related factors.

Implementation of these risk models in daily practice and integration of these models in Computerised Physician Order Entry/Clinical Decision Support (CPOE/CDS) systems is the next step. This creates the possibility to alert the healthcare worker when a patient’s individual risk is high and above a defined cut-off point.

The role of information technology
Patient risk stratification is needed to make the efforts of the hospital pharmacist more efficient. One important condition to be able to focus on high-risk patients with high-risk medication is a further development of more advanced clinical decision support systems to build a safe and efficient medication check for all patients in the hospital.

The CPOE/CDS systems currently used in Dutch hospitals generates a vast number of alerts of drug-drug interactions, duplicate medication and dosing advices. These alerts are only relevant in a minority of cases and often the physician is unnecessarily warned. It is necessary to discuss the relevance of these alerts, the right time that alerts should be
presented and also to which caregiver the alert should be presented (prescriber, hospital pharmacist, pharmacy assistant or nurse). This can improve specificity of the alerts and efficiency of the medication safety process (30). This multidisciplinary discussion should preferably be brought to a national level, so this information can be added to a national standard (G-standard).

More advanced clinical decision support systems combine clinical data of the patient (like laboratory results) with the medication to assess whether for instance dose adjustments should be made in case of renal insufficiency. When these clinical data are included in algorithms, this will lead to more clinically relevant alerts. It is necessary to document these relevant clinical data in electronic health records so they can be made available for this purpose.

In the P-REVIEW study (Chapter 3) we already used a computerized screening method to identify high risk patients, for whom hospital pharmacists performed a medication review. This algorithm was built by combining medication data and clinical data based on recent literature on prescribing errors (3, 31).

Another algorithm, the trigger instrument, was developed to identify possible drug-related problems in the large patient cohort, consisting of a comprehensive set of phenomena such as (change in) laboratory results, medication use, clinical interventions, radiology examinations, consultations of other specialists, transfer to the intensive care unit, readmission within 30 days and death. The major part of the data collection for this trigger instrument was performed automatically, but some of these data were not available in the electronic health records and had to be collected manually. For further development of these kinds of algorithms structured documentation of relevant clinical data of patients in a CPOE-CDSS system is essential. Only then these algorithms can be made applicable for medication surveillance and for extraction of quality indicators related to patient outcomes.

**Organization of healthcare**

A well organized and transparent process of healthcare delivery and a multidisciplinary collaborative care model are important preconditions for safe prescribing of drugs.

Hospital care, nowadays, is characterized by ongoing specialization in medical disciplines and development of new technologies. Elderly, vulnerable patients with multiple co-morbidities requiring multiple drugs intensively consult many different medical specialists and medical residents, who are often rotating in shifts. This fragmentation of healthcare is a challenge for medication safety. The recent report ‘Safe Prescribing must improve’ of the Dutch Inspectorate of Healthcare stated that the “Recommendation on Dividing Responsibilities for Cooperation in Healthcare”, composed by the KNMG in 2010, is insufficiently implemented in daily care practice (32, 33). It is often not clear which physician or pharmacist is responsible for the complete overview of drugs, used by the patient (34). The results of the SURPASS study (Surgical Patient Safety System) have shown the effect of a transparent organization on patient safety in the surgical pathway (35).

In the increasing demand for efficiency in healthcare and continuity of clinical processes, but also because of a shortage of medical residents (MDs), many hospitals have adopted the hospitalist model as a method to cope with this challenges in medical ward care.

Hospitalists are responsible for the delivery and coordination of the daily medical care of hospitalized patients. Their work includes daily ward rounds, performing physical examinations, making decisions regarding necessary tests, treatments and procedures, rendering medical diagnoses and generating and reviewing clinical data. Besides, this ward care is also increasingly reallocated to physician assistants (PAs) (36). A PA is a non-physician healthcare professional licensed to practice medicine in defined domains with a substantial degree of professional autonomy. PAs who are employed for medical care for admitted patients usually work in a team comprising both PAs and MDs (i.e. residents, staff physicians or hospitalists). PAs generally do not rotate and constitute a factor of stability in the continually changing medical workforce. Since January 2013, legislation in Dutch Healthcare authorizes PAs to prescribe medication without supervision. However, data on quality of drug prescribing or adherence to clinical practice guidelines by PAs is not available. We describe the results of a study which aimed to determine the effect of substitution of inpatient care from MDs to PAs on the non-adherence to guidelines on medication prescribing (Chapter 6) (37). This study was conducted as part of a multicenter matched-controlled study comparing wards utilizing a mixed ‘PA/MD model’, on which PAs provided medical care in collaboration with MDs, with wards utilizing a ‘MD model’, on which only MDs provided medical care (38). A set of 17 quality indicators to measure non-adherence to guidelines on medication prescribing by PAs and MDs was composed by 14 experts in a modified Delphi procedure. The indicators covered different pharmacotherapeutic subjects, such as gastric protection in case of use of NSAID or prevention of obstipation in case of use of opioid. In this study 1021 patients from 17 hospital wards in the ‘PA/MD model’ group and 1286 patients from 17 hospital wards in the ‘MD model’ group were included. Two of the 17 quality indicators showed significantly less non-adherence to guidelines for the PA/MD model; the indicators concerning prescribing gastric protection in case of use of NSAID in combination with corticosteroids (OR 0.42, 95% CI 0.19-0.90) and in case of use of NSAID in patients older than 70 years (OR 0.47, 95% 0.23-0.95). For none of the other quality indicators for prescribing of medication a difference between the MD model and the PA/MD model was found. This study suggests that non-adherence to guidelines on medication prescribing on wards with the PA/MD model generally does not differ from wards with traditional house staff by MDs only.

In the next years a further reallocation of tasks concerning prescribing of medication from medical residents and medical specialists to physician assistants, hospitalists and hospital pharmacists can be expected. Giving ongoing specialization of medical disciplines it remains an important task for the hospital pharmacist to support doctors, physician assistants and hospitalists in the prescribing process in multifaceted ways and to monitor quality and safety of prescribing behavior by audit and further research.

**Economic analysis of medication safety interventions**

In the field of medication safety research there is also a growing need for economic analysis of interventions in the hospital organization. More and more, we have to critically monitor costs that are incurred by the hospital as a result of running mediation safety programs in relation to clinical outcome.

In the P-REVIEW study (Chapter 3) we registered the time, spent by pharmacy assistants...
and hospital pharmacists on activities such as checking prescribed medication and interventions performed (16). In the intervention period they also registered time spent on activities such as medication review of high-risk patients and medication safety consultation (MSCs) on the ward. An estimate of the time spent by the prescribing physician to follow up the advice was made. Time spent on the educational program by hospital pharmacists and prescribing physicians of the participating wards during the intervention was also registered.

Costs were calculated by multiplying the time spent on the study-related activities by salary expenditures of healthcare providers, obtained from the collective labor agreement of Dutch hospitals (www.nvz-ziekenhuizen.nl). Not surprisingly, we found that during the intervention, the costs per admission were higher for hospital pharmacists because they performed MSC and ward visits. The costs of pharmacy assistants, however, were lower. We suggested that the educational intervention of the P-REVIEW study proactively intervenes in an earlier stage of the prescribing process, which results in a lesser need of reactive interventions of pharmacy assistants. Taken together, the difference between mean total costs per admission in the usual care period and the intervention period was not statistically significant.

Besides the effectiveness of interventions in clinical practice, the economic impact of the interventions is also very relevant. In our future designs of medication safety research economic evaluation in relation to patient outcome should be taken into account more systematically.

**Medication safety programs in Dutch hospitals**

This thesis described different studies that assess the effect of interventions or the development of tools to improve medication safety. This kind of research should be structurally integrated in medication safety programs in Dutch hospitals. To further improve medication safety in the hospital we must use a multifaceted approach and combine and integrate a range of interventions, such as the interventions described above.

Such interventions should be combined with the development of validated risk prediction tools, enabling risk stratification to make the efforts of these interventions more worthwhile. Knowledge of the high risks, but equally important, acceptance of low risks in the prescribing process can help us to focus safety interventions on high-risk patients and achieve best results in decreasing drug-related problems.

A multifaceted and multidisciplinary strategy allows us to design tailored interventions for different patient categories or patients treated by different medical specialties. Participatory action research (PAR) can assist in implementing the right interventions in the right place. PAR is a research approach to empower healthcare providers to take action to improve their daily clinical care and investigate complex problems in healthcare systems. It is characterized by the involvement of local stakeholders (physicians, hospital pharmacists, nurses) in the identification of opportunities for improved practice, the subsequent development and implementation of tailored interventions directed at these opportunities and the evaluation of the implemented interventions (39).

In case of medication safety research patients are also important participants. The role and responsibility of the patient in medication safety has not been subject of the research described in this thesis. However, it is obvious that (im)patient empowerment deserves our attention as well to improve efficiency and safety of the prescribing process.

Our quality system can support the integration of these interventions and with structural audits and adequate quality indicators, related to patient outcomes, we can introduce a well-functioning PDCA (Plan, Do, Control, Act) cycle. We will be able to monitor the prescribing process and adapt the process if necessary.

Taking into account the huge numbers of medications prescribed and the risks that are associated with the complex process of pharmacological treatment, it will never be possible to completely prevent all drug-related problems. However, by studying the causes of potentially preventable drug-related calamities in our clinical practice, and translating these findings to the care process, we can use these incidents to optimize the system.

The hospital pharmacist has a leading role in the medication safety program in the hospital and in this Participatory Action Research because of the combination of knowledge on pharmacological treatment, science of quality improvement and risk stratification and knowledge of health informatics and process management.

To confirm this role in the future, the training of hospital pharmacists must emphasize (besides obtaining pharmacological expertise) CanMEDS roles such as medical leadership, collaborator and health advocate (40). By leading the improvement of medication safety in organizations and systems, the hospital pharmacist facilitates changes in the prescribing process to enhance clinically relevant patient outcomes. This requires accountability to society and trust and respectful relationships with patients, physicians and other healthcare professionals, community partners and health system stakeholders to establish shared decision making.

**Recommendations for clinical practice**

- To further improve medication safety in the hospital, a multifaceted approach should be used.
- The multifaceted intervention for surgical patients described in the P-REVIEW study is an example of such an approach. It contributes to medication safety and could be implemented in all hospitals.
- Validated risk prediction tools should be introduced, for example the P-REVIEW tool for surgical patients, in our daily clinical practice. Risk stratification in the prescribing process can help us to focus safety interventions on high-risk patients and achieve best results in decreasing drug-related problems.
- We should also label patients who are most unlikely to experience a drug-related adverse event. Acceptance of low risks in prescribing gives us the possibility to downgrade interventions or monitoring for this group of patients.
- Multifaceted tailored interventions must be developed for different wards by involvement of local stakeholders. One size does not fit all.
Implementation of interventions should be routinely evaluated consisting of a continuous process of measuring, audit and feedback on prescribing followed by improving and adopting the interventions and the system.

We need to optimize and update the content of education to the prescriber related to the risk factors for clinically relevant, potentially preventable drug related problems. Introduction of effective educational methods as workplace-based pharmacotherapy education with continuous audit and feedback on the main pharmacological issues and prevailing guidelines will lead to a sustained effect. It may be useful to introduce a “licence to prescribe” for physicians in hospitals.

Not only the development of clinical practice guidelines, but more importantly the implementation and evaluation of these guidelines deserves attention in coming years.

We have to critically monitor costs that are incurred by the hospital as a result of running medication safety programs in relation to clinical outcomes.

For further development of these interventions and evaluation in medication safety programs structured documentation of relevant clinical data of patients in a CPOE-CDSS system is essential.

**Recommendations for future research**

- Participatory action research (PAR) can be used in the identification of suitable recommendations for future research.
- Further development of risk-prediction tools that focuses on specific harmful adverse drug events or on patients with a particular illness of clinical characteristic, has to be performed. Time of risk stratification (in general practice, at hospital admission or during hospital stay) acquires different variables and different models.
- Further development of risk-prediction tools that focuses on specific harmful adverse drug events or on patients with a particular illness of clinical characteristic, has to be performed. Time of risk stratification (in general practice, at hospital admission or during hospital stay) acquires different variables and different models.
- The design of future medication safety studies need robust automated data collection methods and the development of uniform assessments of causal relationships between drug prescribing and patient harm.
- For further development of these interventions and evaluation in medication safety programs structured documentation of relevant clinical data of patients in a CPOE-CDSS system is essential.

**References**


Chapter 8

Appendices

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Chapter 1

General introduction

Although drugs can cure, they can also cause harm. An adverse drug event may result from either appropriate care (non-preventable adverse drug event (ADE)) or from suboptimal care (preventable ADE). Inappropriate prescribing is the most frequent cause of ADEs in the hospital. Prescribing errors can have serious consequences and can lead to potentially preventable death, disability, increased length of hospital stay and readmission. Studies show that up to 20-50% of admitted patients experience one or more adverse drug events during their hospital stay. Approximately 50% of ADEs are potentially preventable. In the last years, older and more vulnerable patients are admitted to the hospital because of transient disease, and they frequently need surgical procedures. Surgical patients have comorbidities, are often treated with multiple high risk drugs and suffer from cognitive and social problems. In case of a surgical procedure, patients are treated with analgesics and antibiotics. Anticoagulant therapy must be temporarily changed because of the surgical procedure. Diuretics and cardiovascular drugs must be adapted on a day to day basis because of rapid alterations of hydration status due to gastro-intestinal disturbances, fever, sweating and lack of intake of fluid and food. These patients are often given radiocontrast for diagnostic procedures. It is known that the complexity of care for these patients contributes to the problem of potentially preventable adverse drug events in the hospital.

The development of a targeted educational programme that covers pharmacotherapy associated with adverse drug events caused by prescribing errors and addresses national and local pharmacotherapeutic guidelines seems useful. This programme should be followed by continuous audit and feedback of the prescriber to boost the effect of education and assures sustainability of knowledge and prescribing behaviour over time. Computerized physician order entry (CPOE) with an integrated clinical decision support system (CDSS) can support both the physician and the hospital pharmacist in clinical decision making. It has been shown to reduce medication errors and even ADEs. However, the specificity of the alerts need to be improved with more advanced CDSS. Also, medication review by clinical pharmacists or clinical pharmacologists is deployed to improve prescribing quality in hospital patients. Hereby a systematic assessment of the medication of the patient is performed in combination with assessment of the clinical data of the patient with feedback to their physician or to the patient. The impact of this approach on clinical outcomes is unknown and performing medication reviews is time consuming.

Clinical practice guidelines with evidence-based recommendations for physicians have been developed to assist doctors and to improve clinician prescribing in hospitalized patients. In routine daily practice however, it appears to be difficult to implement key recommendations and guidelines seem to have a limited ability to change physician prescribing behaviour.

In recent years, hospital care is characterized by increasing demands for efficiency in health care. Implementation of strategies to prevent adverse drug events, that lead to death, disability, increased length of hospital stay or readmission has shown to be worth the effort of clinical pharmacists and prescribing physicians. It is important that interventions, that are designed to prevent prescribing errors are cost-effective. Time spent by the hospital pharmacist and the physician on education, implementation of guidelines, optimal use of CPOE-CDSS or performing medication reviews will also incur cost. Through a change of focus to high-risk patients and less focus on low-risk patients, these interventions could be more efficient.

In the Canisius Wilhelmina Hospital we started a multifacetted approach, combining different safety interventions, to address the problem of prescribing errors leading to adverse drug events. Hospital pharmacists and physicians from the surgical wards of the Isala Hospital and the Meander Medical Centre were willing to adopt this multifaceted approach and to cooperate in the P-REVIEW study (Pharmacist-led Risk patients medication Evaluation to Initiate Event reduction on surgical Wards). The main objective of this thesis is to assess the effect of education and support of prescribing physicians at surgical wards on clinically relevant drug-related complications in hospitalized patients, on guideline adherence and costs.

Chapter 2

The effect of prescriber education on medication related patient harm in the hospital: a systematic review

Prescribing errors defined as “irrational, inappropriate, and ineffective prescribing, underprescribing and overprescribing” caused by a lack of pharmacological knowledge, might be in particular amenable to a clinical pharmacological educational intervention. Therefore, a logical strategy to reduce prescription errors in hospitals is education of prescribers. It is however unclear if education programs actually reduce patient harm. We performed a systematic review that gives an overview of original research papers on education of prescribers, reporting outcomes on (potential) patient harm. A search of the databases Embase and Medline using the Ovid interface was performed. Research on the effect of education of physicians in order to prevent medication related problems of inpatients, reporting original data and outcomes on prescribing errors and/or (potential) patient harm, was included. Assessment of methodological quality and risk of bias was performed using the MINORS checklist and the suggested risk of bias criteria for EPOC reviews. This review shows that only a relatively small number of studies have evaluated the effects of educational programs for hospital physicians, reporting outcomes on (potential) patient harm. Eight studies investigated an intervention on education alone and in 7 studies education was the main part of a multifaceted intervention. All studies were small and had short follow up periods. The educational programs varied and were given to physicians of different specialties and level of experience. Most studies reported intermediate process parameters as outcome. The risk of performance and reporting bias was high. All included studies suffer from poor methodology. The majority, especially studies in which education is part of a multifaceted intervention, report effectiveness on intermediate outcome markers as prescription errors and potential adverse drug events.
There is no firm evidence that educating prescribers in the hospital leads to a decrease of patient harm. However, there is also no sound research showing that education has no effect, and many studies, especially studies with the multifaceted interventions, show benefit on intermediate outcome parameters. Future research should be targeted at development and implementation of educational programs which should be evaluated by high-quality research with outcomes on improvement of patient care. These programs should be a part of a multi-faceted approach in which education is supported by other measures.

Chapter 3

A multifaceted intervention to reduce drug-related complications in surgical patients

The P-REVIEW study was a prospective, multicenter, open intervention study, designed to determine whether a multifaceted intervention of educating the prescriber combined with medication review and pharmaceutical visits to the ward by the hospital pharmacist could lead to a reduction of drug-related complications among surgical patients. After a six-month control period (usual care) the intervention was introduced during three months. This was followed by a six-month intervention period. During the intervention, a combination of an educational programme and medication counselling for prescribers dealing with high-risk patients on the wards took place, in addition to usual care.

An educational programme covering pain management, antithrombotics, fluid and electrolyte management, prescription in case of renal insufficiency and antibiotics was developed. National and local hospital guidelines were included. All prescribers on the participating wards attended the course. Hospital pharmacists performed medication safety consultations, combining medication review of patients who are at risk of drug adverse events and a visit to the physician on the ward. The goal of the visits by the hospital pharmacist was to boost the effects of education and to suggest interventions based on the medication review. To improve feasibility of the intervention, patients who are at risk of drug-related problems, were selected based on medication use and clinical features. Clinically relevant patient outcome measures were studied in a very large patient cohort. Prescription errors, leading to these clinically relevant drug-related problems, were identified in a broad perspective, including possible adverse drug reactions, drug interactions, guideline non-adherence and omission of medication. By blinding all case record forms with respect to the study period before assessment by the experts and by correcting for confounders, the probability of bias was minimised.

6780 admissions of 5940 patients who were admitted to surgical, urological and orthopaedic wards of two large general teaching hospitals in the Netherlands (the Isala Hospital in Zwolle and the Meander Medical Centre in Amersfoort) during the usual care period and 6484 admissions of 5711 patients during the intervention period were included. We found a significantly lower proportion of admissions with one or more clinically relevant, potentially preventable, drug-related problems (including death, temporary or sustained disability, increased length of hospital stay or readmission within 30 days ) in the intervention period (1.1% (73/6484) compared to the usual care period (1.6% (106/6780)) (p=0.029). The relative risk (RR) was 0.72 (95% CI 0.53-0.97). Several types of drug-related problems occurred less frequently during the intervention period, especially haemorrhage, thrombosis and central nervous system events (mainly delirium). Costs incurred as result of time spent on study-related activities by hospital pharmacists, pharmacy assistants and prescribers were not different before and after the intervention. The P-REVIEW study showed that education and support of the prescribing physician with respect to patients who are at risk of drug adverse events in surgical departments leads to a significant clinically relevant benefit for patients without generating additional costs.

Chapter 4

A multifaceted intervention to reduce guideline non-adherence among prescribing physicians in Dutch hospitals

Clinical practice guidelines with evidence-based recommendations for physicians have been developed to assist doctors and to improve patient outcomes. In routine daily practice however, it appears to be difficult to implement key recommendations and guidelines seem to have limited impact on physician prescribing behaviour. Adherence to guidelines by prescribers is inconsistent, despite their potential to improve the quality of health care. Several determinants of practice that prevent or enable guideline adherence, have been described. Interactive and continuous education is one of the possible strategies to tackle several of these determinants for non-adherence.

In the P-REVIEW study we determined whether an approach of introducing an educational programme for prescribers in the hospital combined with audit and feedback by the hospital pharmacist reduces non-adherence of prescribing physicians to key pharmacotherapeutic guidelines. The educational program teaches the prescriber the pharmacological aspects of using high-risk drugs in high-risk patients. The hospital pharmacist performed medication reviews in high-risk patients, who were identified with a computerised screening method. In the visits of the hospital pharmacist to the physician on the surgical ward, there was special attention for adherence to important pharmacotherapeutic guidelines that were addressed in the educational program. Feedback was given based on the medication reviews to the prescriber. The attended issues and advices were discussed in a broader context and hospital pharmacists clarified the pharmacological background and related prevailing hospital guidelines. Patients who were admitted to the surgical, urological and orthopaedic wards of the two hospitals during the fifth month of the usual care period and the fifth month of the intervention period were included.

The outcome measure was the proportion of the admissions of patients in which the physician did not adhere to one or more of the included guidelines. The guidelines were selected by a group of experts and were related to medication that has shown to frequently be involved in preventable, clinically relevant, drug-related problems. 1435 Admissions of 1378 patients during the usual care period and 1195 admissions of 1090 patients during the intervention period were included. Non-adherence was observed significantly less often during the intervention period (21.8% (193/886) as compared to the usual care period (30.5% (332/1089)). The adjusted odds ratio (OR) was 0.61 (95% CI 0.49-0.76).

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This study showed that education and support of the prescribing physician with respect to high-risk patients in surgical departments can lead to reduced pharmacotherapeutic guideline non-adherence among prescribing physicians. Achieved effects were obtained on top of the effect of other measures as CPOE/CDS system and clinical rules, which were part of usual care. However, it may not be necessary to pursue 100% adherence. We suggested it may be better not to focus on guideline adherence or implementation of clinical rules alone, but on a comprehensive medication review of high risk patients, in which a check on adherence of guidelines and clinical rules is integrated.

Chapter 5

Prediction of clinically relevant adverse drug events in surgical patients

Risk stratification of hospital patients for adverse drug events (ADE) would enable targeting patients who may benefit from interventions aimed at reducing drug-related morbidity. It can support clinicians and hospital pharmacists in selecting patients to deliver a more efficient health care service. We performed a study that aimed to develop and test a prediction model that helps to identify patients on the day of hospital admission, who are at increased risk of developing a clinically relevant, preventable adverse drug event during their stay on a surgical ward. Data of the pre-intervention measurement period of the P-REVIEW study were used. Thirty-nine variables, including patient characteristics, type of admission, medication and laboratory test results, were evaluated in a univariate and multivariate logistic regression analysis, respectively. Model performance was expressed in the Area Under the Receiver Operating Characteristics (AUROC). Bootstrapping was used for model validation. 6780 admissions of 5940 patients at surgical wards were included during the pre-intervention period of the PREVIEW trial. 102 Patients experienced a clinically relevant, adverse drug event during their hospital stay that was deemed potentially preventable. The most frequent type of events were haemorrhage, arterial and venous thrombosis, renal insufficiency, hydration or electrolyte related events, central nervous system events and faecal impaction. The prediction model comprised five variables, each ascertained at the time of hospital admission: age, number of biochemical tests ordered, heparin/LMWH in therapeutic dose, use of opioids and use of cardiovascular drugs. The AUROC was 0.86 (95% CI 0.83-0.88). At a cut-off point for an increased risk of developing an ADE of 1.6%, the model had a sensitivity of 80.4% and a specificity of 73.4%. The positive and negative predictive value were 4.5% and 99.6%, respectively. The bootstrap procedure did not significantly affect model parameters.

The combined use of a limited set of easily ascertainable patient characteristics can help physicians and pharmacists to identify, at the time of admission, surgical patients who are at increased risk of developing ADEs during their hospital stay. By using this model, lower-risk patients could be managed less extensively (for instance, only automatically using CPOE/CDS), whereas higher risk patients could receive more intensive interventions, such as medication review, aimed at reducing drug-related adverse outcomes. Such selective use of ancillary precautions could also help to improve the cost-effectiveness of medication safety interventions. In that way, this risk model, that combines clinical and medication-related variables can guide clinical intervention, delivered as part of an integrated system built around the principles of medication safety. This risk model can be incorporated into a CPOE system and thereby generate automatic risk-evaluation based on patients' medical records upon hospital admission. Above a pre-specified cut off point, the score can advise the hospital pharmacist or the prescriber to review the patient's medication or to perform other relevant interventions. Under the cut-off point (not necessarily the same cut off point), it may be possible for the hospital pharmacist to downgrade interventions and rely on the automatic medication safety system.

Chapter 6

The effects of substitution of hospital ward care from medical doctors to physician assistants on non-adherence to guidelines on medication prescribing

In recent years, there is an increasing pressure to deliver healthcare efficiently. Medical procedures are more and more standardized and there is more attention for continuity, quality and safety of clinical processes. Therefore, medical tasks are increasingly allocated to physician assistants (PAs). A PA is a non-physician healthcare professional licensed to practice medicine in defined domains, in collaboration with medical doctors (MDs) but with a substantial degree of professional autonomy. PAs who are employed for medical care for admitted patients usually work in a team comprising both PAs and MDs (i.e. residents, staff physicians or hospitalists). Since January 2012, legislation in Dutch healthcare authorizes PAs to prescribe medication without supervision of a MD. However, scientific evidence on the quality of drug prescribing or adherence to clinical practice guidelines by PAs is hardly available. Until now, there have been no studies to evaluate prescribing of PAs compared to MDs.

In this study the effect of substitution of inpatient care from medical doctors (MDs) to physician assistants (PAs) on non-adherence to guidelines on medication prescribing was determined. This study was conducted as part of a multicenter matched-controlled study comparing wards utilizing a mixed ‘PA/MD model’, on which PAs provide medical care in collaboration with MDs, with wards utilizing a ‘MD model’, on which only MDs provide medical care. The study aimed to measure the effects of substitution of inpatient care from MDs to PAs on length of hospital stay, several indicators for quality and safety of inpatient care and patient experiences. 17 wards of the MD model were matched with 17 wards of the PA/MD model based on medical specialty and hospital type (i.e. academic versus non-academic). A set of 17 quality indicators to measure non-adherence to guidelines on medication prescribing by PAs and MDs was composed by 14 experts in a modified Delphi procedure. The indicators covered different pharmacotherapeutic subjects, such as gastric protection in case of use of NSAID, adequate prescribing in case of impaired renal function, avoidance of certain medication in combination with vitamin K antagonists or prevention of obstipation in case of use of opioids. The outcome measure of this study was the non-adherence to guidelines on medication prescribing measured by 17 quality indicators. The indicators were expressed in proportions by dividing the number of patients in which the prescriber did not adhere to a guideline, by all patients
that were applicable. Multivariable regression analysis was performed in order to adjust for potential confounders. 1021 patients from 17 hospital wards in the ‘PA/MD model’ group and 1286 patients from 17 hospital wards in the ‘MD model’ group were included. Two of the 17 quality indicators showed significantly less non-adherence to guidelines for the PA/MD model; the indicators concerning prescribing gastric protection in case of use of NSAID in combination with corticosteroids (OR 0.42, 95% CI 0.19-0.90) and in case of use of NSAID in patients older than 70 years (OR 0.47, 95% 0.23-0.95). For none of the other quality indicators for prescribing of medication a difference between the MD model and the PA/MD model was found.

From the introduction of the PA there has been debate about prescribing by PAs. It has been suggested that only physicians have the capability to prescribe medication and that only physicians should be allowed to do so. Prescribing is viewed as a very complex, risky clinical task. Many studies have shown that prescription errors made by physicians lead to potentially preventable adverse events in hospitals. Overall, adherence to guidelines varied across the indicators we measured, but tended to be low. This is in line with earlier research on pharmacotherapeutic guideline adherence. Although we have to interpret the results cautiously because of the relatively small sample size for several quality indicators, this study suggested that the non-adherence to guidelines on medication prescribing on wards on which PAs provide medical care in collaboration with MDs (PA/MD model), does not differ from wards on which only MDs provide medical care (MD model).

Chapter 7
Summarizing discussion
The increase in drug consumption by more complex patients has inevitably led to an increase of adverse drug events. Therefore, medication safety has become an important theme in hospitals and several interventions have been introduced to cope with drug-related problems. However, despite all efforts put in medication safety interventions, promoting adherence of professional standards and decreasing shortcomings in organization of care, the potentially preventable harm caused by medication in hospitals did not change. It appears that introducing recommendations, implementing clinical practice guidelines and introducing changes in the healthcare process progress slowly and require a lot of attention and energy of different healthcare providers. Working on medication safety remains a continuous process of measuring, audit and feedback followed by improving and adapting the system and care processes. This thesis describes a multifaceted approach in large teaching hospitals in the Netherlands, combining different medication safety interventions, to address the problem of prescribing errors leading to adverse drug events. In this final chapter the main results are reviewed in a wider perspective in relation to the main objectives of this thesis. First the challenges of the methodology of intervention studies on medication safety are addressed. After that the different components of the multifaceted intervention we studied are discussed. This intervention included education of the prescriber, implementation of guidelines, medication review and the use of information technology. This multifaceted approach must gain focus and be applied in hospitals by using risk stratification in daily practice, imbedded in a good, transparent and efficient organization of healthcare and medication safety programs. These themes are discussed. At the end recommendations for clinical practice and future research are given.
Nederlandse samenvatting

Hoofdstuk 1

Inleiding


Digitale ondersteuning met Computerized physician order entry (CPOE) met een ingebouwd klinisch, beleidsondersteunend beslissingssysteem, kan zowel de arts als de ziekenhuisapotheek helpen bij het nemen van klinische beslissingen. Ook worden medicatieresviews door ziekenhuisapothekers of klinisch farmacologen ingezet om de voorschrijfkwaliteit bij ziekenhuispatiënten te verbeteren. Hierbij wordt de medicatie van een patiënt systematicus beoordeeld in relatie tot de klinische gegevens van de patiënt, waarna er feedback naar de arts of patiënt volgt. Het effect van deze maatregel is echter niet duidelijk en het uitvoeren van deze medicatiebeoordeling is tijdrovend. Ter ondersteuning van de dokter worden er praktische, wetenschappelijk onderbouwde, klinische richtlijnen ontwikkeld met als doel de zorg aan ziekenhuispatiënten te verbeteren. In de dagelijkse praktijk blijkt het echter lastig om deze aanbevelingen te implementeren en blijken richtlijnen maar een beperkte invloed te hebben op het voorschrijfgedrag van de arts. In de afgelopen jaren zien we in de gezondheidszorg een toenemende vraag naar efficiëntie. Het is belangrijk dat de interventies die worden ontwikkeld ter voorkoming van voorschrijffouten ook kosteneffectief zijn. Door patiënten te identificeren die een hoger risico lopen op een ADE, zouden we ons meer op deze hoog- risico patiënten kunnen focussen en minder op de laag- risico patiënten, en kunnen we onze interventies efficiënter inzetten.
Een gecombineerde interventie om geneesmiddel gerelateerde problemen bij chirurgische patiënten te voorkomen

De P-REVIEW studie is een prospectief, multicenter, open interventieonderzoek, dat is uitgevoerd om te bepalen of een onderwijsprogramma aan de voorschrijver gecombineerd met medicatiereviews bij hoog risico patiënten gevolgd door een consult van de ziekenhuisapotheek op de afdeling, kunnen leiden tot een vermindering van geneesmiddel gerelateerde problemen bij chirurgische patiënten. Allereerst werd de standaardzorg gemeten in een controle periode van zes maanden. Daarna werd de interventie geïmplementeerd. Vervolgens werd er gedurende 6 maanden in een interventieperiode gemeten.

Er is een onderwijsprogramma ontwikkeld, waarin onder andere pijnbeleid, antistollingsbeleid, vocht- en elektrolytenhuishouding, het voorschrijven van geneesmiddelen bij verminderde nierfunctie en inzet van antibiotic bij bod komen. De nationale en lokale richtlijnen van ziekenhuizen op deze onderwerpen zijn hierin opgenomen. Alle voorschrijvers van de participerende ziekenhuisafdelingen namen deel aan dit onderwijs. Ziekenhuisapotheek apothekers voerden medicatiereviews uit bij patiënten die een hoog risico lopen op een ADE en combineerden dit met een medisch veiligheidsexamen aan de voorschrijver op de afdeling, waarbij het medicatiebeleid van deze patiënten werd besproken. Met dit consult werd beoogd het effect van het onderwijs te versterken en de richtlijn adherentie te vergroten. De belangrijkste uitkomstmaat van dit onderzoek was het percentage klinisch relevante, potentieel vermijdbare, geneesmiddel gerelateerde problemen bij patiënten die leiden tot overlijden, tijdelijke of blijvende invaliditeit, een verlengde opnameduur of een fatale uitkomsten.

De P-REVIEW studie laat zien dat onderwijs en ondersteuning van de voorschrijvende arts bij hoog risico patiënten op de snijdende afdelingen leidt tot minder vermijdbare geneesmiddel gerelateerde problemen bij deze patiënten zonder dat dit extra kosten met zich meebrengt.
Het voorspellen van klinisch relevante geneesmiddel gerelateerde problemen bij chirurgische patiënten

Risicostratificatie van ziekenhuispatiënten ten aanzien van het optreden van ADE’s, maakt het mogelijk om patiënten te selecteren die mogelijk profijt hebben van interventies met als doel geneesmiddel-gerateleerde morbiditeit te verminderen. Het kan dokters en ziekenhuisapothekers helpen bij het selecteren van patiënten om een zo efficiënt mogelijke zorg te bieden. We hebben een onderzoek verricht met als doel een predictiemodel te ontwikkelen, dat patiënten identificeert op de dag van opname die een verhoogd risico hebben op het ontwikkelen van een vermijdbaar geneesmiddel gerelateerd probleem tijdens hun opname op de afdeling chirurgie, orthopedie of urologie.

Hiervoor hebben we de gegevens uit de controle periode van de P-REVIEW studie gebruikt. 39 variabelen, zoals patiënten kenmerken, soort opname, medicatiegegevens en laboratoriumuitslagen werden gebruikt voor de bouw van het model met behulp van logistische regressieanalyse. Model prestaties werden uitgedrukt in de Area Under the Receiver Operating Characteristics (AUROC), 6780 opnames van 5940 patiënten op chirurgische afdelingen werden geïncludeerd. 102 patiënten hebben tijdens hun verblijf in het ziekenhuis een klinisch relevant ADE gehad, die mogelijk voorkomen had kunnen worden. De meest voorkomende bijwerkingen waren bloedingen, arteriële en veneuze trombose, nierinsufficiëntie, hydratie- of elektolytengerateleerde problemen, klachten van het centrale zenuwstelsel en obstipatie. Het predictiemodel bestaat uit vijf variabelen, vastgesteld bij het moment van ziekenhuisopname: leeftijd, aantal aangevraagde biochemische testen, heparine/LMWH in therapeutische dosis, gebruik van opioiden en het gebruik van cardiovasculaire medicijnen. De AUROC was 0.86 (95% BI 0.83-0.88). Bij een afkappunt van 1.6% voor een verhoogd risico op het ontwikkelen van een bijwerking, had het model een sensitiviteit van 80,4% en een specificiteit van 73,4%.

De positieve en negatieve voorspellende waarde waren respectievelijk 4,5% en 99,6%. De combinatie van een klein aantal gemakkelijk te bepalen patiëntkenmerken helpt artsen en apothekers om bij opname chirurgische patiënten te identificeren, die een verhoogd risico hebben op het ontwikkelen van een ADE. Door dit model te gebruiken kunnen laag-risico patiënten minder intensief gecontroleerd worden (bijvoorbeeld alleen automatisch met CPOE/CDSS), terwijl we hoog-risico patiënten meer intensief kunnen bewaken, zoals met medicatiereview.

Dit selectieve gebruik van ondersteunende voorzorgsmaatregelen door de inzet van een predictiemodel vergroot de kosteneffectiviteit van interventies gericht op medicatieveiligheid. Dit risicocmodel kan worden opgenomen in een CPOE systeem, om zo een automatische risico inschatting te maken aan de hand van de medische gegevens bij ziekenhuisopname. Een score boven een vooraf bepaalde afkapwaarde kan de ziekenhuisapotheker of arts adviseren om de medicatie van de patiënt te reviewen of andere relevante interventies uit te voeren. Bij een score onder de afkapwaarde (niet noodzakelijk dezelfde afkapwaarde) kan de ziekenhuisapotheker controles verminderen en varen op het automatische medicatieveiligheidssysteem.
uitvoeren. Er zijn veel studies beschikbaar die laten zien dat door artsen gemaakte voorschrijffouten leiden tot vermijdbare ADE’s in ziekenhuizen. Hoewel we voorzichtig moeten zijn met het interpreteren van de resultaten vanwege de relatief kleine steekproefomvang voor de verschillende kwaliteitsindicatoren, suggereert dit onderzoek dat de non-adherentie aan de farmacotherapeutische richtlijnen niet verschillend is op afdelingen met een ‘PA/arts model’ in vergelijking met afdelingen met een ‘arts model’.

Hoofdstuk 7

Afsluitende discussie
De toename van geneesmiddelengebruik bij complexere patiënten heeft onvermijdelijk geleid tot een toename van ADE’s. Hierdoor is medicatieveiligheid een belangrijk thema geworden in ziekenhuizen en zijn er verschillende strategieën geïntroduceerd in een poging geneesmiddel-gerelateerde problemen te vermijden. Ondanks alle inspanningen die zijn geleverd om de medicatieveiligheid in ziekenhuizen te vergroten, zoals het aansturen op het naleven van professionele richtlijnen en het verminderen van tekortkomingen in zorgorganisaties, is de door geneesmiddelen veroorzaakte vermijdbare schade in ziekenhuizen onveranderd gebleven. Het introduceren van veranderingen in het zorgproces verloopt traag en vraagt veel aandacht en energie van verschillende zorgverleners. Het werken aan medicatieveiligheid blijft een continu proces van meten, audit en feedback, gevolgd door het verbeteren en aanpassen van zorgprocessen.

Dit proefschrift beschrijft een meervoudige aanpak in perifere opleidingsziekenhuizen in Nederland, waarbij verschillende interventies gericht op medicatieveiligheid gecombineerd worden, om het probleem van voorschrijffouten die leiden tot ADE’s aan te pakken. In dit afsluitende hoofdstuk worden de belangrijkste resultaten in een breder perspectief bekeken, in relatie tot de belangrijkste doelstellingen van dit proefschrift. Allereerst worden de uitdagingen van de methodologie van interventiestudies naar medicatieveiligheid behandeld. Daarna worden de verschillende componenten van de meervoudige interventie die we onderzocht hebben besproken. Deze bestond uit onderwijs aan de voorschrijver, het implementeren van richtlijnen, medicatiereview en het gebruik van informatietechnologie. Deze meervoudige aanpak kan worden toegepast in ziekenhuizen door risicostratificatie in de dagelijkse praktijk te gebruiken, ingebed in een werkzame, transparante en efficiënte gezondheidszorgorganisatie en in programma’s voor medicatieveiligheid. Deze thema’s worden besproken. Tot slot worden aanbevelingen gedaan voor de klinische praktijk en toekomstig onderzoek.
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Beste André, jij was, samen met Judith, de trekker van de P-REVIEW studie in Zwolle. Je hebt als lid van het onderzoeksteam heel wat reisjes naar Nijmegen gemaakt en meegedacht in de uitvoering van het onderzoek en de analyse van de resultaten. Hartelijk dank hiervoor.

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Beste Elsbeth, jij bent vanaf de start een groot voorstander geweest van dit onderzoek en was een enthousiast deelnemer van het onderzoeksteam. Tot op de dag van vandaag zie ik jou als de grootste fan van het P-REVIEW concept (op mij na dan). Ik wil je hartelijk danken voor je inzet, deskundige bijdrage en vertrouwen.

Hans Pot heeft de P-REVIEW database gebouwd. Beste Hans, in een driemanschap van jou, Kees en mijzelf hebben we uitdagende welke wijze we de data uit de deelnemende ziekenhuizen zouden gaan verzamelen, valideren en beheren. De combinatie van jouw kennis van het gebied van ICT en farmacologie was onmisbaar. Ik ben blij dat je na het onderzoek in opleiding bent gegaan tot ziekenhuisapotheker in het MeanderMC en je inmiddels ook in het UMC in Utrecht je kwaliteiten hebben ontdekt. Ik wil je danken voor je inzet en ik wens je een succesvolle loopbaan toe.

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List of publications

**Publications presented in this thesis**


**Poster presentations and oral communications of the P-REVIEW study**

The 1th Annual Congress of the Netherlands Organisation for Health Research and Development (ZonMw), 31 januari 2013 in Utrecht, the Netherlands (Oral communication)

The 12th Congress of the European Association for Clinical Pharmacology and Therapeutics (EACPT 2015), 27-30 June 2015 in Madrid, Spain (Poster).

Figon Dutch Medicines Days 2015, 5-7 October 2015 in Ede, the Netherlands (Poster)

Hospital Pharmacy Days 2017, 9-11 November 2017 in Bunnik, the Netherlands (2 Oral communications, nomination for best abstract)

The 13th Congress of the European Association for Clinical Pharmacology and Therapeutics (EACPT 2017), 24-27 June 2017 in Prague, Czech Republic (Oral communication)

Figon Dutch Medicines Days 2017, 2-3 October 2017 in Ede, the Netherlands (Poster)
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About the author

Jacqueline Maria Bos was born on September 5th, 1967 in Brielle and grew up in Rosmalen, the Netherlands. After graduating from secondary school (Gymnasium) at the Jeroen Bosch College in ’s-Hertogenbosch in 1985, she started her study Pharmacy at the University of Utrecht. In 1991 she obtained her Master of Science degree and in 1993 her Pharmacist’s degree.

In the same year she worked as a pharmacist in the Canisius-Wilhelmina Hospital in Nijmegen. From 1994 to 1997 she was trained as a hospital pharmacist in the VU University Medical Center in Amsterdam (supervisor: drs A.C. van Loenen). After this specialization she kept working in the VU University Medical Center.

In 1998 she started working as a hospital pharmacist in the Canisius-Wilhelmina Hospital in Nijmegen. In 2007 and 2008 she worked for two years at the division of Pharmacoepidemiology & Clinical Pharmacology of the Department of Pharmaceutical Sciences, Utrecht University where she performed a research project with Prof dr. A. de Boer and Prof. dr. M. L. Bouvy.

In 2010 Jacqueline became trainer of hospital pharmacists in the Canisius-Wilhelmina Hospital in Nijmegen. Her interest in clinical pharmacology and medication safety resulted in performing the PhD research described in this thesis. Her PhD research was conducted in collaboration with the Department of Pharmacology and Toxicology of the Radboud University Medical Center in Nijmegen.

Jacqueline is married to Raymond Braakhuis and has three children: Ties (18), Cato (16) and Anouk (14).
Improving medication safety in surgical patients  
Impact of a multifaceted intervention  

Jacqueline Maria Bos  