Medication safety in older inpatients: Measurement and intervention strategies
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“If we wait for the moment when everything, absolutely everything is ready, we shall never begin.”

Ivan Sergejevitsj Toergenjev
In the next ten years the percentage of older people (aged 65 years or over) in the total population is projected to increase by more than 40%. As a consequence, older people will constitute the majority of patients visiting healthcare professionals. Appropriate prescribing for older patients is challenging because of often present multimorbidity, polypharmacy, cognitive decline, and altered physiological functions. The objective of this thesis was to assess medication safety in older hospitalized patients by measuring adverse drug events (ADEs) and by applying a set of explicit quality indicators (QIs), second to develop and implement a multifaceted intervention strategy (MFIS), and third to investigate the effect of this strategy on preventable ADEs and ADE recognition in older inpatients. This objective is captured by three main projects included in this thesis: the Intensive Care Unit (ICU) study (Chapter 4.1), Assessing in-hospital pharmaceutical Care Of Vulnerable Elders in the Netherlands (ACOVE-NL; Part 3), and Ward-oriented pharmacy In Newly admitted Geriatrics Seniors (WINGS) study (Part 2, Chapter 4.2, and Part 5).

In this final Part 6 the results of these studies will be put into a broader perspective. First, the challenges of measuring medication safety will be further discussed. Second, our 4-step approach used as a framework for developing and implementing medication safety interventions will be evaluated. Finally, the implications of this thesis for hospital and hospital pharmacy practices and future research will be presented.

MEASURING MEDICATION SAFETY

The diversity in methodology to measure medication safety as presented in this thesis is not uncommon in this field of research. Although there is a widely acknowledged need for standardization of definitions and outcomes assessment, an approach suited to the aim(s) of a study, setting(s) in which the study needs to be conducted, and study resources available (in terms of money and infrastructure) can not be disregarded. In other words, one size does not fit all.

METHODS BASED ON PATIENT OUTCOMES

In this thesis ADEs were used to measure medication safety and to evaluate effects of medication safety interventions. Lessons learned from these studies about ADE identification and assessment processes can provide directions for reliable and efficient future use of ADEs as an outcome measure.

Definitions

In the WINGS and the ICU study we applied an internationally accepted definition for an ADE:

'any harm occurring during the patient’s drug therapy and resulting either from appropriate care, or from unsuitable or suboptimal care. Adverse drug events include: the adverse drug reactions (ADRs) during normal use of the medicine, and any harm secondary to a medication error, both errors of omission or commission; i.e., preventable ADEs'.

However, within this ADE definition, there is a wide discrepancy in what is considered to constitute ‘harm’. In a large study on adverse events in older inpatients by Thomas and colleagues harm was defined as either prolonged hospital stay or disability at discharge. In contrast, in the WINGS and the ICU study, definition of harm was not limited to such severe cases. This discrepancy is one of explanations for
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the high ADE yield gained in the WINGS study.\textsuperscript{10} One could argue that such approach inflates the results on ADE incidence. Nevertheless, disregarding mild or moderate harm as an ADE could lead to underestimation or even missing of ADEs with potential to cause severe patient harm. For example, the clinical course of constipation due to use of a narcotic without a laxative will in most patients result in mild discomfort quickly resolved by prescribing a stool softener. Although much less frequently, in some patients constipation could however result in severe confusion requiring prolonged hospital stay.\textsuperscript{11} The same applies for events such as electrolytes disturbances or raised creatinine, frequently identified in the WINGS study and often causing mild to moderate harm. Therefore, a less conservative approach to what constitutes harm seems more appropriate, especially in high-risk and/or vulnerable patients, or whenever a detailed insight on ADE occurrence is needed.

Furthermore, an ADE can result in different outcomes of harm, notably: in the worsening of an existing pathology, in the lack of any expected health status improvement, in the outbreak of a new or to be prevented pathology, in the change of an organic function, or in a noxious response due to the medication taken.\textsuperscript{8} Based on results of various ADE studies in older inpatients, it seems that usually only outbreak of new harm is considered.\textsuperscript{12-15} Yet, by including all of the above mentioned types of harm outcomes in the WINGS study, we identified for example several cases of worsening of or delayed recover from infection caused by inappropriate choice of empirical antibiotic therapy. These preventable and clinically relevant ADEs would be missed if we only focused on new harm. For this reasons, others have also advocated to include wide variety of harm outcomes.\textsuperscript{16}

\textbf{What to measure?}

Most ADE studies in hospitalized patient focus either on ADE occurrence upon admission or during the hospital stay.\textsuperscript{17} However, especially in older inpatients, recognition of ADEs could be hampered and should be investigated.\textsuperscript{3,16} Therefore, in the WINGS study for all ADEs identified (upon admission and during the hospital stay) the recognition by medical teams involved was assessed. We found that of ADEs present upon admission and also of ADEs occurring during the hospital stay, 20\% was not recognized by medical teams.\textsuperscript{19} Consequently, a valuable insight when developing intervention strategies was gained.

When measuring ADEs as defined earlier, ADRs and preventable ADEs will be identified. ADRs are assumed not preventable and therefore, from medication safety point of view, these outcomes are less relevant as they can not be reduced by interventions. However, precisely this non-responsiveness to interventions makes ADRs a suitable validity measure. In the WINGS study the rate of ADRs (non preventable ADEs) per 100 hospitalizations remained constant throughout the whole study period (p = 0.86), while the rates of preventable ADEs and unrecognized ADEs were significantly reduced (both p < 0.001). On top of reliability assessment, these results reassured us that our expert team was consistent in ADE judgments, and that the effect measured was related to reduction of outcomes expected to be affected. The latter advantage of measuring ADRs is especially valuable when less robust study designs such as before-after design or interrupted-time series are chosen. In medication safety research such designs are very common as parallel control groups are often very hard to identify.\textsuperscript{7}
ADE identification and assessment

One of most profound difficulties in ADE identification arises from the fact that for an event to be assessed as related to drug commission or omission, causal relationship needs to be established. For that purpose, several causality algorithms have been proposed but none has been accepted as the ‘gold standard’. Use of structured and standardized algorithms may in theory result in a systematic and therefore consistent and reproducible causality assessment. However, as clinical judgment is required at various stages of the causality assessment, it is hard to entirely rule out subjectivity in this process. This is especially the case for the evaluation whether or not other factors such as disease or patient related factors may have contributed to the event.

Older inpatients included in the WINGS study had on average three chronic diseases and were using on average seven medications upon admission and eleven medications during the hospital stay. Assessing the criterion “other factors” was therefore a challenging endeavor, similarly to assessing preventability, i.e., was an event caused by a medication error. So far, no standardized method for assessing ADE preventability has been developed. In line with many other ADE studies, our experts have assessed preventability based on what is known from pharmacotherapeutic guidelines and formularies. Because scientific evidence to guide pharmacotherapeutic choices in older patients is limited, assessing preventability, still often relies on clinical judgment.

Therefore, to minimize bias due to subjectivity of the ADE assessment process, it is important to ensure that the same experts assess ADEs across study sites and during whole study period. Because ADE assessment includes judgment on drug specific and disease/patient specific variables, it seems self-evident that experts with medical as well as medication knowledge should both be appointed for ADE assessment and agree upon ADEs included.

To improve reproducibility of ADE identification we applied two explicit tools during ADE identification and assessment. The first was an adapted Institute for Healthcare Improvement (IHI) ADE trigger-tool, developed in the United States (US) to identify ADEs in general inpatient population. Although the advantage of this tool in terms of reproducibility was also identified in the WINGS study, its low ADE sensitivity in older inpatients (only 36% of ADEs was related to a trigger) proved to be a major drawback. In contrast, the use of the Common Terminology Criteria for Adverse Events v3.0 (CTCAEv3) for severity grading can be advocated. By applying this explicit tool we gained almost perfect intra- and inter-rater reliability (κ = 0.93 and κ = 0.85 respectively) for ADE severity judgements. Use of CTCAEv3 had no influence on ADE yield gained.

METHODS BASED ON PROCESS OUTCOMES

As shown by the results of the WINGS and the ICU study, measuring medication safety by using ADEs as outcome measure and patient chart review as method to identify ADEs is a powerful approach to gain detailed insight in how often patients are actually harmed by the care we provide, how often this harm could have been prevented, and to what extent preventable harm was reduced by implementing interventions. Also, we found that reliability of this approach can be improved by using CTCAEv3, structuring the ADE assessment process, and appointing the same team of experts. The ADE yield of this approach can be significantly increased by
using the proposed definitions for an ADE, harm, and harm outcomes, and by appointing both a physician and a pharmacist as experts.\textsuperscript{10,27}

These efforts to improve reliability and sensitivity of ADE measurement came however at a price: an estimated two hours per patient were needed for research nurses and students to gather information from patient charts, and for skilled medical experts to review this information and assess if ADEs have occurred. Therefore, for 500 patients included in the WINGS study, approximately 125 full-time working days were required to complete data collection; an investment clearly not feasible in routine practice. For this reason, along with developing an ADE-based method we also developed a method based on explicit process outcomes (Chapter 3.1). The reliability of the developed QI set was almost perfect (\( \kappa = 0.85 - 0.88 \)). Furthermore, the set was easily applicable by pharmacy students taking on average 45 minutes per patient to complete the set.\textsuperscript{29}

Subsequently we applied this QI set to assess in-hospital pharmaceutical care in 200 older inpatients and found that continuity of care, monitoring of drug therapy, and prescription of indicated medication urgently needs improvement (Chapter 3.2). Yet, no differences between high and low quality score groups as assessed by this QI set were found with regard to 500-day survival or readmissions within 90 days.\textsuperscript{30} To be valid, the confirmation of a relationship between explicit process outcomes and patient outcomes is critical. This condition needs to be satisfied to assure that interventions aimed at aspects of medication safety identified as poor by explicit process outcomes (such as QIs) will have a significant role in reducing negative patient outcomes (such as preventable ADEs).\textsuperscript{31}

Consequently, based on these findings one could conclude that the developed explicit set of 87 QIs, even if proven reliable and feasible\textsuperscript{29}, cannot be used as an alternative for the laborious and more subjective ADE-based method presented in Chapter 2.1. Before drawing such a conclusion one should however take in consideration that, as mentioned earlier, patient outcomes such as readmission and mortality can be influenced by many factors such as characteristics of the patient, the prescriber or underlying disease(s).\textsuperscript{31} As the reasons for readmissions and mortality were not registered, readmissions and mortality with no relationship to aspects of care measured by the QIs may have diluted the contrast between the high and low quality score groups. In addition, the dilution of contrast could be increased by the fact that some of the QIs included were based on expert opinion rather than on clinical evidence.\textsuperscript{30}

**WHICH SIZE FITS WHOM?**

Based on the knowledge gained on the merits and the limitations of ADE- and QI-based methods, the following guidelines for selecting an appropriate method can be proposed:
<table>
<thead>
<tr>
<th>ADE-based method</th>
<th>QI-based method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Setting</strong></td>
<td>No insight in the occurrence and type of medication related harm</td>
</tr>
<tr>
<td><strong>Primary goal of measurement</strong></td>
<td>Research</td>
</tr>
<tr>
<td><strong>Process most likely to be pinpointed</strong></td>
<td>Prescribing</td>
</tr>
<tr>
<td><strong>Preconditions</strong></td>
<td>Patient charts are detailed and easily accessible.</td>
</tr>
<tr>
<td></td>
<td>A systematic and structured case report form (CRF) to conduct chart review is available. Adapted IHI ADE trigger-tool can be used as an aid but not for patient-pre-selection.</td>
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<tr>
<td></td>
<td>A systematic and structured ADE assessment CRF is available.</td>
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<tr>
<td></td>
<td>The same pair(s) of experts is/are appointed for the entire study.</td>
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<td></td>
<td>The expert pairs consist of pharmacists and physicians.</td>
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<td></td>
<td>Use an ADE definition which includes ADRs and preventable ADEs due to drug omission and commission.</td>
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<td></td>
<td>Harm outcomes include new harm, worsening of harm, sustained and prolonged harm.</td>
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<td></td>
<td>Use CTCAE to assess ADE severity.</td>
</tr>
<tr>
<td><strong>Directions</strong></td>
<td>Both ADEs present upon admission and ADEs occurring during the hospital stay should be included in the measurement to assess ADE recognition by medical teams.</td>
</tr>
<tr>
<td></td>
<td>Especially when detailed measurement and/or medication safety assessment in high-risk patients is required, all severity grades of harm should be included.</td>
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<tr>
<td></td>
<td>Especially when less robust study designs are chosen, ADRs can be a valuable validity measure and their rate should be identified.</td>
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<tr>
<td></td>
<td>It is always necessary to periodically study the ADE rate, especially when workflows in an organization are substantially changed or new ones introduced.</td>
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FRAMEWORK FOR IMPROVING MEDICATION SAFETY FOR OLDER INPATIENTS

Dr. Atul Gawande, American surgeon and journalist widely known as an expert on reducing error and improving safety in healthcare, claims hospital leaders need five skills to tackle patient safety: they need to “collect data to recognize failure and success, develop solutions to problems based on that data, implement solutions effectively, identify the most important projects, and lead the organization through the process.”

To tackle medication safety in older hospitalized patients, in this thesis, these five skills were translated into a framework which included the following four steps:

**Step 1:** Comprehensive ADE measurement was conducted.
**Step 2:** Based on local ADE data, multidisciplinary risk analyses were organized to determine failing or lacking safety nets in the prescribing process in the participating hospitals, and to develop interventions.
**Step 3:** Barriers related to implementation of the proposed interventions were identified and addressed.
**Step 4:** A multifaceted intervention strategy (MFIS) was successfully implemented in three hospitals during a period of nine months.

Implementation of MFIS resulted in a significant reduction of 51% in the rate of all preventable ADEs and a 63% reduction in the rate of severe preventable ADEs occurring during the hospital stay, and a significant 52% reduction in the rate of unrecognized ADEs in older inpatients. In comparison to other ADE intervention studies in older inpatients, the effect of MFIS was superior.

A number of insights arose from applying this tailored approach which might benefit others. These insights can be grouped into facilitators and barriers to improvement of medication safety in older inpatients.

**FACILITATORS**

The availability of local ADE data as a starting point for the development of MFIS, appointing a senior Internal Medicine specialist next to a pharmacist to identify and assess ADEs, and multidisciplinary effort in conducting risk-analyses and designing interventions were all valuable in gaining support and cooperation of internal medicine and ICU physicians for implementing interventions. However, two factors were critical to the success of implementing MFIS: 1) the participation of Internal Medicine residents in multidisciplinary risk-analyses, and 2) a selection of interventions at different levels of prescribing process linked to preventable ADEs (multifaceted) and within local budget and possibilities.

During the multidisciplinary risk-analyses, the Internal Medicine residents not only expressed their concerns about the unsafe system-based conditions but also about their own limited pharmacotherapy knowledge and the need for more feedback on medication prescribing. The main unsafe system-based conditions derived were: inadequate clinical decision support system (CDSS) generating an overload of clinically irrelevant alerts, limited supervision by attending physicians on medication prescribing, and time constraints on delivery of inpatient care. The type of feedback the residents felt to be beneficial was the active role of hospital pharmacists in medication prescribing and education about geriatric pharmacotherapy. The majority
of residents working in all three participating hospitals had one to two years of clinical experience. Gaps in geriatric pharmacotherapy knowledge and skills are of major concern across all care settings and levels of medical experience. An open attitude from these young professionals was exceptional, given the often-present (and, in the opinion of the author of this thesis, inappropriate) stigma associated with medical errors. By creating a safe environment during the risk analyses and by putting the emphasis on problem solving and shared responsibilities between pharmacists and physicians for older inpatients’ pharmacotherapy, we achieved a constructive discussion with focus on medication safety.

Given the multiple causes related to the occurrence of preventable ADEs as extracted during the risk analyses, it was obvious that one single solution to improve medication safety in the often vulnerable and complex older inpatients would not be sufficient. However, it is often the case that interventions for tackling different threats to medication safety will exceed the resources available, making it impossible to implement all putatively effective interventions at a certain time. In hospitals, where resources in terms of money and people are scarce, prioritizing interventions is therefore required.

At the time of WINGS pre-measurement, in all three hospitals Computerized Physician Order Entry systems with a standard CDSS (CPOE-CDSS) were operating. Based on our results, it seems that the CPOE-CDSS systems in place were an effective safety net in preventing ADEs related to drug-drug interactions and duplicate therapy, as only 8% of preventable ADEs were caused by these types of medication errors. However, these systems were failing in preventing errors such as prescribing of contraindicated medications, omission of indicated medication, and overprescribing. These medication errors were frequent in our and many other studies in older patients. Furthermore, these systems generated an overload of clinically irrelevant alerts and were usually overridden by physicians. Various studies showed that this is the case for 49% to 96% of the alerts generated by similar CPOE-CDSS. Therefore, the need expressed by medical residents for a more advanced CDSS was not surprising. An advanced CPOE-CDSS includes dosing support for renal insufficiency and geriatric patients, guidance for medication-related laboratory testing, and drug-disease contraindication checking. However, at the time of the WINGS study, the participating hospitals had no budget available to replace the existing CPOE-CDSS systems with more advanced ones.

As a surrogate intervention, the medical residents proposed a pocket-sized checklist of the most frequent medication-related problems in older inpatients, based on pre-measurement of the WINGS study. The aim of this checklist was to provide the residents with an easy-to-use tool to enable them to conduct a quick check on the appropriateness of pharmacotherapy of their patients.

The need for a more active involvement of hospital pharmacists in medication prescribing presented itself with a different challenge: changing the practice of hospital pharmacists and physicians. In the Netherlands as well as in most European countries, hospital pharmacy practice is more product- and research-oriented than clinically patient-focused, and hospital pharmacists are scarce. Therefore, hospital pharmacists are usually available only on call for medication advice, a reactive approach. However, an active daily participation of hospital pharmacists in medical teams on the wards (these pharmacists are usually referred as clinical pharmacists)
has been shown to reduce morbidity, preventable ADEs, and medication errors in older inpatients.\textsuperscript{23,38,45-48} In mainly Anglo-Saxon countries, where clinical pharmacy is an established practice, clinical pharmacists are considered experts in the therapeutic use of medication and are recognized as providing a unique set of knowledge and skills to the health care system, and are therefore qualified to assume the role of drug therapy expert.\textsuperscript{49-51}

In the Netherlands, the physicians are not used to on-ward collaboration with pharmacists, and for many physicians the role of hospital pharmacists as drug therapy expert is less clear. Therefore, it was first necessary to address these barriers in order to examine if implementation of clinical pharmacy in the participating Dutch hospitals would be feasible.\textsuperscript{52}

The study conducted on the ICU (Chapter 4.1) provided us with valuable clues on how clinical pharmacy practice can successfully be translated to the Dutch hospital setting.\textsuperscript{27} We found that the reduction in preventable ADEs achieved by active on-ward participation of a hospital pharmacist in multidisciplinary patient review meetings on the ICU on average three days per week was comparable to reduction achieved by daily full-time on-ward participation of clinical pharmacists in the US hospital setting.\textsuperscript{27,53,54} Also, appointing senior hospital pharmacists with ICU pharmacotherapy knowledge to conduct medication reviews and subsequently discuss the identified potential medication-related problems with the ICU physicians, were factors which may have contributed to the high acceptance rate of the provided advice (74\%) and the overall positive effect of the intervention.\textsuperscript{27} When conducting medication reviews the ICU hospital pharmacists used structured screening forms which were designed based on their experience from the pre-measurement phase. These aspects of the ICU intervention strategy were adapted for the WINGS study.

To further increase feasibility of medication reviews in daily practice, next to senior hospital pharmacists, hospital pharmacy residents and pharmacy students were also appointed to help. To increase flexibility, the outcomes of the medication reviews were discussed face-to-face with the residents involved instead during multidisciplinary patient review meetings.

The quick-win intervention was the geriatric pharmacotherapy education for medical residents. Based on ADE results from the WINGS study, a presentation about the do’s and don’ts when prescribing for older patients was designed. This presentation was given within a standard training schedule for medical residents, so no organizational changes were required and time needed was limited to two to four sessions of a half hour each.

The result of the above described process was a strategy consisting of three types of medication safety interventions implemented simultaneously and aiming to close the gaps at different levels of the prescribing process:

- geriatric pharmacotherapy education,
- pocket-sized medication problems checklist,
- comprehensive medication review by a hospital pharmacy team followed by on-ward face-to-face feedback on prescribing, on average 3 days per week.

This strategy is illustrated in Figure 1.
BARRIERS

In comparison to two leading studies in the general hospitalized patient populations on clinical pharmacist on-ward participation in medical teams (78% reduction in preventable ADEs in the study by Kucukarslan and colleagues56, and 68% reduction in the study by Leape and colleagues54), the effect of MFIS (51% reduction in preventable ADEs) was slightly lower. This lower effect may be described by aspects related to the present hospital and hospital pharmacy care practice.

When a patient is admitted to the hospital, the standard approach is to primarily focus on the reason(s) for admission and issues secondary to this reason. This focus on problems of an acute nature is related to the relatively short duration of hospital stay. The compression of the length of stay is a trend in hospital care destined to continue.57 Furthermore, often when older patients are admitted to a hospital, medical teams are confronted with many (chronic) medications prescribed prior to hospitalization by many other physicians. Because older patients’ clinical condition can quickly deteriorate, a once-beneficial medication could become less appropriate and should be (re)evaluated.3 Also, inconsistency of prescribing patterns of different physicians are of great concern. This inconsistency is mainly related to the disease-centered focus of medical care and lack of guidelines for prescribing in multimorbid patients.58

To be able to address issues related to the medication regimen in its entirety, sufficient knowledge of geriatric pharmacotherapy and medicine, involving other specialists in shared decision making, and collaboration with outpatient caregivers
such as general practitioners (GPs) are required. The above outlined barriers may explain the reluctance of medical residents in accepting and enforcing advice related to home medication regiment, medication prescribed by “others” or advice not related to the reasons of admission/acute problems. This reluctance was a frequent topic of discussion between hospitals pharmacists involved in the MFIS.

To effectively address medication related problems, hospital pharmacists participating in on-ward medical teams, need to master clinical skills such as sufficient knowledge of patient- and disease-related factors in relationship to patient’s symptoms, and verbal and written inter-professional communication. Also, sufficient time is needed to establish a relationship built on trust, understanding and sharing knowledge between physicians and pharmacists.52,59

Yet, the current hospital pharmacy residency program in the Netherlands is still largely focused on back-office activities such as drug production, medication logistics, and managerial tasks. Sporadically, hospital pharmacy residents get the opportunity to spend a limited amount of time on the wards and gain some experience in collaborating with physicians and nurses. Once hospital pharmacists are registered, the large amount of time consumed by the back-office activities and the limited number of hospital pharmacists per department leaves a fraction of time which can be diverted to on-ward patient-related activities. Furthermore, at present only one two-day training with a focus on verbal and written inter-professional communication is included within the whole four-year hospital pharmacy residency curriculum. When enquired about collaboration with hospital pharmacy teams involved in the MFIS, medical residents often mentioned communication skills of the pharmacist involved and unclear clinical relevancy of advice as factors hampering acceptance.

SUSTAINABILITY OF MEDICATION SAFETY IMPROVEMENTS
It is widely recognized that healthcare safety improvements require a system perspective to identify and level out barriers, such as the emphasis on production, the emphasis on autonomy and craftsmanship of healthcare professionals, the lack of arbitration to optimize safety strategies, and the general complexity of health care processes.60

The recently repeated analyses of adverse events in Dutch hospitals showed that between 2004 and 2012, important reductions of avoidable patient harm have been achieved in the fields of diagnostics, surgical interventions, invasive procedures and general care. However, such improvement is glaringly absent in the field of medication safety, since the incidence of medication-related adverse events have remained unchanged during this period.61 One of the causal factors is probably the fact that medication safety improvements, such as those presented in this thesis, are more difficult to achieve because they often require multidisciplinary effort and a rearrangement of medication workflows and responsibilities. Enforcing such changes long-term requires leadership of hospital boards and investments on that level.62

Yet, the current reimbursement for hospital care in the Netherlands is mainly based on “fixed price per day” and “paying for production” structure. Therefore, cost avoidance, for example from reduction of the length-of-stay, or reduction in monitoring, procedures, or medication use by prevention of medication errors and
ADEs, will not lead to direct savings for the hospital. Also, potential savings gained by such interventions from prevention of ADEs after hospital discharge and from a societal perspective (for example lost labour force productivity) are not at all represented by this reimbursement structure. It is clear that such a structure acts prohibitively on a routine implementation of medication safety improvements.

This was illustrated by the study conducted in two nursing homes (Chapter 5.2) where an MFIS was implemented with an aim to reduce administration errors in nursing home residents with swallowing difficulties. We found that the effect on crushing uncancellable medication (a high risk medication error) was maintained long-term. However, the effect on other relevant medication errors, such as using an incorrect technique when crushing medication and the occurrence of food-drug interactions, was not because extra and skilled manpower was needed to rearrange medication administration workflows in the nursing homes in this study. Similar, although the WINGS and the ICU interventions were feasible to maintain when under supervision of the research team, the component ‘medication reviews and on-ward face-to-face feedback three times a week’ proved to be challenging to maintain in the daily practice. The time investment needed to gather information on patients’ medical history and present complaints from patient charts, conduct reviews, document interventions, and follow-up on advice required a dedicated full-time hospital pharmacist. Such a position was not sustainable long-term within the available hospital pharmacist staffing.

It appears that, in spite of ample proof of efficacy, effectiveness and most probably also cost-effectiveness, the MFIS and ICU intervention strategies have not been fully implemented in the daily practice, not even at the hospitals participating in these studies. In the opinion of the author of this thesis, a paradigm shift is needed to gain meaningful and sustainable improvements in medication safety.

First, not the cost savings but patient harm avoidance and quality of care should be the main incentives for hospital boards to implement medication safety interventions. Recently, LL M André Rouvoet, the chairman of Dutch healthcare insurance companies’ branch organization (Zorgverzekeraars Nederland), announced that he wants to change the way hospitals are reimbursed for their costs, from “paying for production” to “paying for quality”. The quality of healthcare should be the main focus for insurers and healthcare providers. In the US, big insurance companies have already been introducing this concept across the country. Second, hospitals should be more transparent about their level of medication safety and implement mechanisms enabling them to track medication safety progress over time. Third, and perhaps most important, patients need to be made more knowledgeable about which hospitals have excellent medication safety, and demand continuous quality improvements.

**IMPLICATIONS FOR CLINICAL PRACTICE**

To our knowledge, the results of two main projects: the WINGS and the ICU studies, presented in this thesis, are the first in providing insight into occurrence and types of ADEs and their preventability and recognition in these high risk inpatients for the Dutch hospital setting. Furthermore, the effects of ward-oriented pharmacy interventions on these outcomes were not previously evaluated in the Netherlands for ICU patients and internationally for older inpatients. The WINGS study received
considerable attention in the media, and was elected by the Dutch Healthcare Inspectorate (IGZ) as one of the top ten patient safety projects in the Netherlands in 2011. To gain meaningful improvements in medication safety, hospitals should create a culture of constant learning from mistakes among health care professionals, and use the proposed framework to develop and implement interventions. Interventions which have impact on present workflows, require multidisciplinary involvement, and changes in organizational culture and practice are less likely to succeed if not carefully planned and in compliance with the resources available.\textsuperscript{65}

HOSPITAL CARE PRACTICE FOR OLDER INPATIENTS
The main question that needs to be answered is: who is in charge of pharmacotherapy in its entirety in the often multimorbid polymedicated older inpatients? To be able to answer this question we need to shift the current disease-centered focus of health care to a patient-centered focus. Instead of managing all individual diseases and medication related to them, we should aim to maximize the health goals of individual patients and with that aim choose the most appropriate medication.\textsuperscript{58} In order to achieve this aim, two aspects of current hospital care for older inpatients should be rearranged.

First, because no one medical specialist can possibly have all of the skills required to integrate medication and patient-related problems across all medical conditions, and within the context of each patients’ health goals, risks and priorities, the multidisciplinary team approach seems to be the best approach to deliver safe care for older inpatients.\textsuperscript{58} As shown by the WINGS and ICU study, hospital pharmacists should be involved in such teams. Hospital pharmacists oversee the medication regimen from a patient-centered rather then disease-centered perspective and can, therefore, be seen as pharmacotherapy generalists.

Second, to secure continuity of care, integrating patient care across health care settings is important in all aspects of medicine, but there is a pressing need to address this in older patients, who often have multiple (co)morbidities. General practitioners should be involved in shared decision making while their patients are hospitalized. Communication to general practitioners and outpatient pharmacies about the course of hospitalization and changes in medication and/or disease management should be detailed and delivered shortly after discharge.\textsuperscript{66} Responsibilities and actions across settings related to medication monitoring and follow-up post-discharge should be made explicit, and exchange of relevant clinical patient information (for example laboratory values) should be accomplished. Within the current medical curricula, gaps in skills and knowledge related to care for older patients should be addressed.\textsuperscript{67} Hospital pharmacists can assist in pharmacotherapy education not only for medical students but also for medical residents.

HOSPITAL PHARMACY PRACTICE
To gain the full potential of hospital pharmacists’ knowledge in improving prescribing for older but also other inpatients, this knowledge should be applied in practice by close and long-term on-ward collaboration with physicians and nurses. In the ICU study we found that the acceptance rate increased from 60% during baseline to 74% during the intervention period, which illustrates the learning effect of such collaboration. Therefore, the hospital pharmacy residency program should allow for at least 6 months of active participation of hospital pharmacy residents in medical teams on the wards, with a minimum of 3 days per week. Training with focus on
clinical skills should be intensified, especially since hospitals are increasingly implementing integrated electronic hospital record (EHR) systems and pharmacists are documenting their advice and interventions directly in patients’ records.

Because the back-office activities are the fundament of each hospital pharmacy department, their continuity and quality must be secured. Consequently, hospital pharmacists should invest in development of tools and in changing workflows to empower themselves in engaging in on-ward patient consultations in an efficient and effective manner.

Health information technology (HIT) holds great promise to achieve this goal. HIT medication safety interventions have been shown to reduce potential and real errors in medication processes while at the same time providing cost-effective care. In the Netherlands, several so called ‘clinical rules’ have been developed and disseminated by the Dutch Hospital Pharmacists Association (NVZA). These clinical rules are a form of advanced CDSS and combine data from the EHR (e.g., laboratory findings, patient characteristics), the CPOE (medication use) and the ‘G-standard’ (National Dutch drug database), and can be used by hospital pharmacists as medication surveillance tool to select patients at risk for possible ADEs. For example, a clinical rule which generates alerts based on patient specific renal function and medication dosing would be very valuable, given the type of preventable ADEs identified in the WINGS study. One should, however, bear in mind that when prescribing for older patients, factors such as multimorbidity, patients’ physical and cognitive functions, life expectancy, quality of life, and patients’ goals of care need to be taken into account when selecting appropriate medications. Therefore even with most advanced HIT solutions in place, clinical judgment will always be necessary.

Furthermore, in recent years, the role of pharmacy technicians in the Dutch hospital setting is shifting to more front-office clinical tasks such as medication reconciliation on admission and at discharge, and educating nurses on safe parenteral medication preparation on the wards, with promising results. On international level as well, pharmacy technicians’ valuable role in improving medication safety is increasingly being acknowledged. Therefore, hospital pharmacists should involve pharmacy technicians in clinical tasks. In order do so, like the hospital pharmacists, the pharmacy technicians should receive more training in clinical skills. An example of such training is the recently-introduced pharmacy practitioner course. Instead of waiting for implementation of advanced CDSS, pharmacy technicians should be appointed for initial screening for clearly defined potential drug-related problems, such as the use of narcotics without a laxative, more frequent monitoring of the INR when drug-drug interactions are not avoidable, or inappropriate dosing according to renal function. By doing so, a first check on the appropriateness of prescribing could be provided, allowing hospital pharmacists’ scarce time to be devoted to less clearly defined and complex pharmacotherapeutic issues like those mentioned before.

**IMPLICATIONS FOR FUTURE RESEARCH**

The proposed shift from “paying for production” to “paying for quality” for the way hospitals are reimbursed for their costs by insurance companies (as announced by André Rouvoet and already introduced in the US), urgently raises the need for valid medication safety outcome measures and for implementation of interventions with high potential to effectively and sustainably reduce negative patient outcomes.
ADEs. A reduction of preventable ADEs tracked over time is the best way to show definitions and tools used to identify them. These efforts are required in order to be further improve validity and reproducibility of ADE-based methods, and agree on safety interventions.\(^7,8^0\) Such a model should especially be considered for ‘mixed methods model’, to evaluate medication safety or effects of medication research. Researchers should use a range of outcomes and different data sources, the so-called however, medication safety is a complex phenomenon. Consequently, hospitals and researchers should use a range of outcomes and different data sources, the so-called ‘mixed methods model’, to evaluate medication safety or effects of medication safety interventions.\(^7,8^0\) Such a model should especially be considered for multifaceted intervention strategies to link effects or lack of effects to specific components included in such complex strategies. Therefore, instead of appointing explicit process outcomes as an alternative for ADEs, use of QIs as an additional source of information seems more appropriate. For example, by scoring QIs we identified that medication information in discharge letters (continuity of care domain) was very poor. This poor quality of in-hospital pharmaceutical care has been associated with preventable ADE occurrence after discharge.\(^8^1\) Because in the WINGS...
study only ADEs present on admission or occurring during the hospital stay were measured this relevant aspect of medication safety, was not identified as needing improvement.

Although, several studies have been conducted on the effects of multidisciplinary teams on improving outcomes in older inpatients, few have focused on medication safety and hospital pharmacists were rarely included in such teams. Also, studies which examine the effect of shared responsibilities in medication management between hospital and outpatient pharmacists are lacking. Future evaluations of such complex interventions should include sustainability assessment and cost-effectiveness analyses including cost savings from a hospital’s and a societal perspective.

Because multidisciplinary teams or hospital pharmacists cannot be involved in the care of every patient admitted to a hospital, computerized tools, such as clinical rules, should be explored as components of multifaceted intervention strategies in order to assist physicians and nurses in ADE prevention and recognition. However, because at present the positive predictive value (PVV) and rule effectiveness of many clinical rules is suboptimal, the alerts generated are first seen by hospital pharmacists and not by physicians. Usually, more data about patients pre-selected by clinical rules need to be gathered in order to evaluate if an alert is clinically relevant. Therefore, first further research is needed to improve clinical rules’ effectiveness and PVV, and to develop clinical rules which could replace the basic G-standard-based alert system and be used by physicians at the time of prescribing. In addition to the clinical rules, once validated, use of computerized QIs seems not only a promising tool to track medication safety but also to assist physicians in patient monitoring and preventive screening.

In the meantime, physicians could simply include ADEs in the list of differential diagnoses when admitting older inpatients with polypharmacy and involve hospital pharmacists, who are available on call 24/7 for medication advice, in the subsequent medication analysis.

As proposed by Jerry Avorn, professor of medicine at Harvard Medical School, Boston (US): “Discovering that a symptom is caused by a drug presents an uncommon opportunity to effect a total ‘cure’ by stopping the offending prescription or lowering the dose.” There is no time to waste.
REFERENCES


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