Medication safety in older inpatients: Measurement and intervention strategies
Klopotowska, Joanna

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IMPROVING MEDICATION SAFETY IN OLDER INPATIENTS

Measurement and intervention strategies

Adverse drug events (ADEs) are the second most common type of patient harm caused by healthcare management rather than by the patients' underlying disease process. ADEs have been associated with hospital readmissions, increased length-of-stay, and mortality, and lead to substantial medical costs. Despite these gloomy realities, the fact that majority of ADEs is preventable is the most encouraging. Once a hospital has an insight in its weak spots in medication safety, intervention(s) to repair these weak spots can be implemented in order to prevent medication errors and reduce preventable ADEs (pADEs) related to these errors. So far, the most sensitive strategy to identify ADEs is a comprehensive patient chart review (PCR) by skilled medical experts. This strategy is however time consuming, depends on implicit clinical judgment which often hampers reproducibility of ADE results. Also, under-detection is likely to occur if such review is not structured. Therefore, (explicit) ADE trigger-tools to improve reliability and sensitivity of a PCR, and measures based on explicit process outcomes (i.e. quality indicators, QIs) rather than on patient outcomes have been advocated as alternative approaches to measure medication safety.

Older patients (65 years and older) experience far more ADEs compared with younger adults. Characteristics such as polypharmacy, multimorbidity, impaired cognitive and physical functions, often present in older patients, may all attribute to this higher ADE risk. These characteristics make appropriate prescribing and recognition of ADEs in older inpatients a challenging endeavor. In the Netherlands, as well as in many other countries, the daily medical care of older inpatients is usually provided by junior medical residents who are supervised by attending senior physicians. When making prescribing decisions, medical residents depend on their and their supervisors' pharmacotherapy knowledge, and on medication guidelines and protocols. In most Dutch hospitals basic Clinical Physician Order Entry combined with Clinical Decision Support System (CPOE-CDSS) are in place which generate drug-drug interaction alerts, duplicate orders alerts, and general dosing advice. However, overload of clinically irrelevant alerts generated by such basic CPOE-CDSS is a major limitation and may even lead to error-producing situations. Furthermore, gaps in geriatric pharmacotherapy knowledge and skills are of major concern across all care settings and levels of medical experience. In addition, within the current Dutch hospital pharmacy practice hospital pharmacists are usually only available on-call for pharmacotherapy consultations (i.e. reactive approach).

Although results from published studies can provide clues how to improve prescribing for older inpatients, each hospital should first identify its own medication safety problems in this process. Second, local ADE data should be analyzed with professionals involved in the medication prescribing process to determine which safety nets are lacking or at risk of failure, and to develop interventions. Interventions having multidisciplinary commitment are more likely to succeed. Third, once an intervention strategy is chosen, barriers in implementing this strategy in daily practice should be listed, and an approach to tackle these barriers should be set. This is especially important when such interventions are multifaceted and/or demand major changes in current workflow. Finally, the effect of the intervention...
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strategy implemented should be evaluated and future directives should be determined. This 4-step approach is the framework of this thesis.

The main objectives of this thesis were to determine medication safety in older inpatients by measuring ADEs and by applying QIs, to develop and implement a multifaceted intervention strategy (MFIS), and to investigate the effect of this strategy on preventable ADEs and ADE recognition in older inpatients

PART 1: GENERAL INTRODUCTION
Part 1 provides the scope, objective and outline of this thesis. In this general introduction section an overview of the complexity of medication safety measurement and achieving appropriate prescribing in older inpatients, and a framework for the development and the implementation of medication safety interventions, are presented.

PART 2: ADVERSE DRUG EVENTS IN OLDER INPATIENTS
Part 2 of this thesis describes an ADE measurement strategy based on a structured PCR and the results gained by this strategy when applied for ADE identification in a cohort of older hospitalized patients.

In Chapter 2.1 we investigated the ADE occurrence in older inpatients admitted to internal medicine wards of the three participating Dutch hospitals (one academic and two non-academic institutions). In the 250 included older inpatients (65 years and older and taking ≥5 medications on admission), our expert team identified 118 ADEs which occurred in 62 patients. This ADE yield was 1.1 to 2.7 times higher in comparison to other ADE studies in older inpatients. Of the 118 ADEs, 71% was preventable and 43% caused serious preventable patient harm. Patient harm caused by ADEs resulted in various types of events (clinical signs/symptoms as well as laboratory abnormalities).

Aspects of our ADE identification strategy such as the use of the ADE trigger-tool as an aid during the PCR, a broad scope of definitions utilized, and appointing a physician as well as a pharmacist as an expert may all explain the high ADE yield gain. Also, our structured and systematic process resulted in a reliable ADE measurement by the same team of experts: the overall intra-rater agreement was substantial (agreement between judgments by the same expert team at two separated time points). However, gaining sufficiently high inter-rater reliability proved to be challenging: the overall inter-rater agreement was only fair (agreement between judgments of two different expert teams). Although ADE trigger-tool has the potential to improve inter-rater reliability, its low ADE specificity in older inpatients (only 36% of ADEs were related to a trigger) proved to be a major drawback. Prescribing contra-indicated medications, over- and undertreatment, and dosing errors were the most frequent prescribing errors related to pADEs identified. These prescribing errors occurred despite safety nets in place such as: CPOE-CDSS, supervision by the attending physicians, and on-call availability of hospital pharmacists.

Understanding physicians’ ability to recognize ADEs in older inpatients is another important aspect of medication safety. This insight is needed to ensure that medication regimens are optimized and harm obviated on time. Therefore, in Chapter 2.2 we studied ADE recognition by the medical teams in the same group of
older inpatients included in the study presented in Chapter 2.1. We found that of the
ADEs already present upon hospital admission 20% was not recognized by the medical
teams. Furthermore, 20% of ADEs occurring during the hospital stay was also missed.
Moreover, unrecognized ADEs (uADEs) were significantly more often preventable ADEs
\((p < 0.001)\). ADEs with evident causality and with clinically apparent and severe
consequences were far better recognized in comparison to ADEs mimicking underlying
pathologies, with lower severity, or resulting only in abnormal laboratory values.
However, achieving timely recognition of such less critical and less evident ADEs
should be aimed for to prevent future emergencies.

**PART 3: QUALITY OF CARE IN OLDER INPATIENTS**

Part 3 of this thesis describes development and validation of a method based on
explicit QIs and the results gained by this method when applied for the assessment of
quality of care in older inpatients.

In Chapter 3.1 the adaptation of the Assessing Care Of Vulnerable Elders (ACOVE) QIs
set [developed in the United States of America (USA)] to measure the quality of in-
hospital pharmaceutical care of older patients (ACOVE-NL) is presented. The
development process consisted of three review rounds. Each round consisted of a
process of modification and formulation of QIs by the two designated pharmacists,
followed by an expert panel review of content and face validity. The final QI set
developed included 87 QIs of which 49 were based on ACOVE QIs and 38 were newly
added. This ACOVE-NL QI set demonstrated excellent inter-rater reliability and good
feasibility. The lowest \(\kappa\) value measured was 0.85 (range: 0 to 1, with zero for no
agreement and 1 for almost perfect agreement).

In Chapter 3.2 the developed ACOVE-NL QIs set was applied to measure the quality
of in-hospital pharmaceutical care in a cohort of 200 older inpatients admitted to a
tertiary 1002-bed academic hospital in the Netherlands. For each patient QIs were
scored using medical record data and discharge letters, and pass rates per indicator
were calculated (percentage of patients who received care according to formulated
criteria). We found that 3 out of 4 domains of pharmaceutical care were of
suboptimal quality: ‘Prescribing indicated medication’ with median pass rate of 64%,
‘Continuity and documentation’ with median pass rate of 20%, and ‘Monitoring of
Medication’ with median pass rate of 37%. However, according to the indicators a
better quality of pharmaceutical care was not associated with an improved 500-day
survival and fewer readmissions within 90 days.

**PART 4: CONCEPTUALIZING AND DESIGNING WARD-ORIENTED
PHARMACY**

Results of well-controlled studies suggest that in particular, clinical pharmacy and
multidisciplinary team interventions can improve medication prescribing in older
inpatients. Clinical pharmacy refers to daily on-ward participation of clinical
pharmacists in medical teams (active approach); a standard practice in most Anglo-
Saxon countries. In contrast, in Dutch as well as in most European hospitals, hospital
pharmacists are often only available on call for medication consultations (reactive
approach), and hospital pharmacy practice is more product and research-oriented
than clinically patient-focused. Furthermore, hospital pharmacists are scarce (for
example: in the USA there is on average 18.1 full-time equivalent available for
pharmacists per 100 occupied hospital beds whereas in Europe there is 0.9 full-time

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**Chapter 2.1**

Chapter 2.2

Chapter 3.1

Chapter 3.2

Chapter 4.1

Chapter 5.1

Chapter 6.1

Chapter 7.1

Summary
equivalent available for pharmacists per 100 occupied hospital beds). For these reasons, we cannot directly transfer the successful clinical pharmacy concept to the Dutch hospital setting. Yet, given the results presented in Part 2 and 3 of this thesis, an active on-ward involvement of Dutch hospital pharmacists seems desirable.

In Chapter 4.1 the results of a pilot study on an Intensive Care Unit (ICU) of a tertiary 1002-bed academic hospital in the Netherlands are presented. This study was conducted to examine whether ‘ward-oriented’ pharmacy, a clinical pharmacy concept tailored to the Dutch hospital setting as defined in this thesis, can be equally effective in reducing preventable ADEs and medication errors as compared to settings in which clinical pharmacy is well established. We found that by conducting medication reviews by hospital pharmacists on average three days per week and by discussing the identified potential medication related problems directly with the ICU physicians during on-ward patient review meetings, ward-oriented pharmacy substantially reduced the number of all prescribing errors and those that resulted in patient harm (77% and 100% reduction, respectively). These results were comparable with the findings of two leading studies on the effects of clinical pharmacy on ADEs in the United States of America. Furthermore, the additional costs of ward-oriented pharmacy (as described in this study) seem to be well outweighed by the savings which resulted from more appropriate drug therapy.

In Chapter 4.2 the protocol of Ward-oriented pharmacy in Newly admitted Geriatric Seniors (WINGS) study is presented. This protocol was designed based on our experiences gained on the ICU with regard to the implementation of ward-oriented pharmacy concept in the Dutch hospital setting and to aspects of ADE measurement and assessment. In this chapter we outlined our implementation strategy which included gaining a multidisciplinary commitment and tailoring an intervention strategy to specific needs and resources of the participating hospitals.

PART 5: MULTIFACETED INTERVENTION STRATEGIES
In Part 5 of this thesis, the results of two multicentre studies in older (in)patients, one in a hospital setting and one in a nursing home setting, are presented. In these studies multifaceted intervention strategies were implemented to improve medication safety in older (in)patients. These strategies included ward-oriented pharmacy approach.

In Chapter 5.1 we studied the effect of a multifaceted intervention strategy (MFIS) on pADEs and on ADE recognition in older inpatients. A total of 500 inpatients aged 65 years and older and admitted to internal medicine wards of one academic and two non-academic hospitals in the Netherlands were included, equally divided between a baseline and an intervention measurement period and in compliance to short interrupted time series design. Based on local ADE data, multidisciplinary teams in each participating hospital conducted risk-analyses and developed a tailored MFIS. The MFIS consisted of three complementary interventions implemented simultaneously: a comprehensive medication review followed by face-to-face feedback on prescribing by hospital pharmacists, geriatric pharmacotherapy education, and a pocket-sized checklist of drug-related problems for internal medicine residents.

We found that the rate of pADEs occurring during the hospital stay per 100 hospitalizations was reduced by 51% ($P < 0.001$), the rate of serious pADEs per 100
hospitalizations by 63% \( (P < 0.001) \), and the rate of uADEs per 100 hospitalizations by 52% \( (P < 0.001) \). In total, 81% of the reduction in pADEs during intervention period was attributable to less use of contra-indicated medications, and fewer dosing and inappropriate choice errors. The hospital pharmacists involved in the MFIS made a total of 400 medication recommendations of which 62% were accepted by the medical teams. Although the MFIS proved to be a powerful approach to substantially improve medication safety in older inpatients, barriers related to the current disease-oriented hospital practice and product- and research-oriented hospital pharmacy need to be tackled in the near future to be able to reduce medication related harm in older patients even more effectively and sustainably.

**Chapter 5.2** describes implementation of an MFIS specifically designed to reduce medication administration errors (MAEs) in nursing home residents with swallowing difficulties. This strategy included: education for nursing staff about crushing medication safely, a medication administration protocol for patients with swallowing difficulties, a ‘do-not-crush-medication’ pocket card for the nursing staff, screening of medication charts by pharmacy technicians on potential crushing problems, and advices on medication charts on safe medication administration to residents with swallowing problems. The effect of this strategy was assessed by measuring the number of MAEs per number of observed medication administrations during a pre-intervention and implementation period (short- and long-term).

We found that the number of crushing uncrushable medication errors (an MAE subtype with the highest potential risk for patient harm) was reduced by 63% short-term \( (p = 0.005) \) and 53% long-term \( (p = 0.045) \). However, the reduction in the overall number of MAEs gained short term (24% reduction, \( p = 0.035 \)) was not identified long-term (11% reduction, \( p = 0.493 \)) primarily because extra and skilled manpower was needed to rearrange medication administration workflows in the nursing homes. Such investment proved to be not achievable at the time of this study.

**PART 6: GENERAL DISCUSSION**

Part 6 provides a general discussion of the results of the individual studies in this thesis placed into a broader perspective. Three topics are discussed: the measurement of medication safety by using ADEs as patient outcome and by using QIs as process outcome, a framework for improving medication safety for older inpatients by using an approach based on a 4-step model, and the sustainability of medication safety improvements. Furthermore, the implications for practice and future research are outlined.

Improving medication safety in hospitalized patients is a challenging endeavor because medication safety interventions often require multidisciplinary effort and a rearrangement of medication workflows and responsibilities. Therefore, enforcing such changes long-term requires leadership of hospital boards and investments on that level. Given the complexity of medication prescribing in older patients, involving multiple (in- and outpatient) care-providers and interventions at various levels of the medication prescribing process (in- and outpatient) are necessary to achieve appropriate pharmacotherapy tailored to individual risks, needs and goals of therapy of an older patient. To measure progress in medication safety over time, tracking ADEs and process outcomes such as QIs seems most appropriate.