Medication safety in older inpatients: Measurement and intervention strategies
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"If we always do what we’ve always done, we will get what we’ve always got."
Adam Urbanski
PART 1
GENERAL INTRODUCTION
It's now 15 years since the United States (US) Institute of Medicine's landmark 1999 report To Err Is Human put patient safety prominently on the international agenda. Of patients admitted to hospitals, 3.7% to 17.7% inadvertently experience adverse events (AEs) by the way their healthcare is delivered.\(^1,2\) An AE is usually defined as an unintended injury or complication resulting in patient harm and caused by healthcare management rather than by the patient's underlying disease process. Aside from the direct harm to the patient, AEs are a considerable financial burden to the healthcare system. The annual direct medical costs in Dutch hospitals were estimated at a total of €355 million for all AEs and €161 million for preventable AEs in 2004.\(^3\)

Studies on the occurrence of AEs during hospitalization showed that adverse drug events (ADEs), i.e., medication related harm, are the (second) most common type of AEs.\(^2,4,5\) An ADE is usually defined as any harm ful event occurring during drug therapy and resulting either from appropriate care (non-preventable ADEs) or from medication errors (preventable ADEs).\(^6\)

**MEDICATION SAFETY IN HOSPITALIZED PATIENTS**

Studies on ADEs in hospitalized patients tend to group patients into two categories: those with ADEs developed in the outpatient setting and present upon or causing admission to a hospital, and those who develop an ADE during their hospital stay.\(^7\) The prevalence of hospital admissions associated with ADEs ranges from 0.1 to 54%.\(^8–10\) Studies on ADE incidence during hospitalization report that 6 to 58% of hospital patients experience one or more ADEs.\(^11–14\) Differences in setting, study population, definitions applied, and detection method used may all contribute to these highly variable results.\(^8\)

**CHOOSING ADE IDENTIFICATION STRATEGY**

The methods to collect data on ADEs include non-stimulated or stimulated self-report, patient chart review (PCR), manual or computerized ADE trigger-tools, direct observation, or a combination of methods. Every method has a different ADE yield and detects a somewhat different subset of ADEs.\(^15\)

A PCR is considered a gold standard for ADE detection because of its high ADE yield and its specificity in detecting preventable ADEs.\(^16,17\) First, usually trained nurses, pharmacists, or physicians manually review patient charts to identify possible events. Next, during expert panel meetings, the reviewers discuss and assess all suspected ADEs on the following three aspects:

1) **Causality**: what is the relation between disease, drug effect or lack of effect, and an event?

2) **Severity**: how serious was the patient harm related to the ADE identified?

3) **Preventability**: was the ADE caused by a medication error?

Several criteria, standards, and definitions can be applied to assess these aspects. Most tools rely on reviewers' understanding of the complex data found in the medical records (i.e., judgment-based or implicit approach).\(^18\) As a consequence an ADE assessment has a high degree of subjectivity, often resulting in variability between results generated by the reviewers.\(^16,19\) Furthermore, a PCR is time consuming, and ADEs can be easily missed when such review is unstructured. To circumvent these...
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limitations, use of explicit (criterion-based) ADE identification tools has been proposed to measure ADEs more efficiently and reliably.

The most widely advocated is the Institute for Healthcare Improvement (IHI) ADE trigger-tool.\textsuperscript{20,21} This trigger-tool consists of 23 triggers or sentinel words which could indicate the occurrence of an ADE, for example ordering of antidotes, certain abnormal laboratory values, and abrupt medication stop orders.\textsuperscript{22} First, patient charts are screened using this trigger-tool in a manual or computerized version. Only charts with positive triggers are then further reviewed in detail by pharmacists and/or physicians to assess if actual ADEs have occurred; this strategy spares reviewers’ time. Furthermore, the reviewers’ search is more structured, resulting in less variability and less chance of missing ADEs.\textsuperscript{16,22}

QUALITY INDICATORS
Another approach to measure medication safety is an approach based on explicit process measures rather than on patient outcome measures such as ADEs. Explicit process measures assess whether care provided accords with accepted standards. These measures are quality indicators (QIs). QIs are explicitly phrased IF-THEN criteria usually derived from published reviews, expert opinions, and consensus techniques.\textsuperscript{23} For example, prescribing a long-acting benzodiazepine for insomnia in a patient with a history of falls indicates poor quality of care. The main advantage of explicit QIs in comparison to ADEs is the fact that they can be readily applied with little or no clinical judgment to large samples of people, and have shown to gain reliable results.\textsuperscript{24}

WHERE TO START?
From a medication safety perspective, preventable ADEs are the most relevant subset of ADEs, as medication errors can in theory be eliminated. The studies on ADE incidences report rates of preventability at up to 57\% for ADEs occurring in hospitals and of almost 70\% for ADEs leading to hospital admission.\textsuperscript{15,25} Figure 1 illustrates the relationship between ADEs and medication errors.

Approximately 1\% of all medication errors actually results in ADEs.\textsuperscript{15} Most medication errors have no or minimal potential to cause harm (minor medication errors, e.g., 500 mg of acetaminophen was given two hours too late) or have the potential to cause harm but actual harm does not occur either because of specific circumstances, chance, or because such errors are intercepted and corrected (potential ADEs, e.g., an overdose of morphine is intercepted by the pharmacist).\textsuperscript{16} Medication errors and related preventable ADEs can occur at any stage of medication process: reconciling, prescribing, transcribing, dispensing, administering, and monitoring. Although all medication errors should be considered as opportunities to learn and to reduce the risk of similar errors recurring, medication errors at the prescribing stage seem to be the most clinically relevant because they more often result in patient harm compared to errors in other medication processes.\textsuperscript{25,27}
Part 1

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Older patients (65 years and older) experience far more ADEs compared with younger adults. Although it is controversial whether or not age itself is an independent risk factor for ADEs, older patients may be at higher risk for ADEs because of several other patient-related factors often present in this population. These factors include polypharmacy (often defined as use of 5 or more chronic medications), multimorbidity, impaired renal function, cognitive impairment, non-adherence to drug regimen, and dependant living situation (e.g., a nursing facility). Polypharmacy is the most consistently reported risk factor for ADEs in the literature. Furthermore, ADEs seem to be more common in the intensive care and internal medicine wards, probably due to the case mix of patients admitted to these wards (higher severity of illness, many comorbidities), and intensive use of (high-risk) medication often requiring careful pharmacologic monitoring.

PRESCRIBING FOR OLDER PATIENTS

Pharmacootherapy for patients of any age can often be complex but prescribing for older patients offers special challenges. These challenges arise from the fact that polypharmacy in older patients is more frequent than in younger patients, mainly because of increased prevalence of chronic medical conditions in this population. This characteristic makes older patients more prone for drug-drug interactions and significant harm arising from them. Furthermore, many medications need to be used with special caution because of age-related changes in pharmacokinetics (PK) that can affect drug absorption, distribution, metabolism, and excretion. The most profound PK change in older patients is the reduction in renal drug elimination. Therefore, an age-dependent decline of total clearance is to be expected for all medications that are predominantly eliminated by the kidneys, and their dose should be adjusted accordingly.
In addition to PK, pharmacodynamics (PD) may also be altered in older patients. Age-related changes in PD may occur at the receptor or signal-transduction level, or homeostatic mechanisms may be attenuated.\textsuperscript{32,33} The central nervous system is a particularly vulnerable drug target in older patients which predisposes them to an increased frequency and severity of extrapyramidal symptoms and anticholinergic effects of for example psychoactive medications. Decrease in homeostatic mechanisms increases susceptibility of older patients to side-effects such as postural hypotension as a response to use of blood-pressure lowering medications, dehydration when using diuretics, and oversedation or respiratory depression when using narcotics.\textsuperscript{32}

While the physician cannot alter the characteristics of individual patients which influence PK/PD, he or she is in charge when making decisions whether to prescribe anything at all, which medication to choose, and how it should be used (e.g., dose and duration of therapy). These decisions should be consistent with patients’ goals of care, treatment targets, time until benefit for a specific disease-drug combination, and the condition of a patient.\textsuperscript{34} However, selection of the right medication and dose for an older patient is hampered because of the scarcity of research evidence to guide these choices.\textsuperscript{35} Especially, for those patients suffering from several chronic diseases; i.e., multimorbidity, choosing the most appropriate pharmacotherapy may be a hard puzzle to solve. Also, when a drug is selected, regular monitoring should be conducted to recognize ADEs in time and preclude further harm. ADE recognition can be challenging because side-effects of many drugs are nonspecific and can mimic underlying disease processes. This is especially the case in older patients who often present with atypical signs and symptoms.\textsuperscript{36,37}

**IMPROVING PRESCRIBING FOR OLDER INPATIENTS**

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, residents depend on their and their supervisors’ pharmacotherapy knowledge, medication guidelines, and protocols to guide these decisions. When a decision is made, a prescription is written. In the Netherlands, use of computerized physician order entry (CPOE) to prescribe medication is a common standard. Usually once to twice daily the attending physicians discuss medical and pharmacotherapy care plans with the residents, followed by additional actions if necessary. Physicians specialized in geriatric medicine and hospital pharmacists are mostly available on-call for consultations (reactive approach).

Given the relatively short duration of the hospital stay, appropriate prescribing for older inpatients (i.e., following guidelines like those presented in Box 1) may be an improbable reality. Also, due to increasing complexity of medical practice and technology, it is challenging to stay up-to-date with all the latest treatments and protocols.
**BOX 1 GUIDELINES FOR GOOD PRESCRIBING IN OLDER PATIENTS.**

- Carry out a regular medication review and discuss and agree all changes with the patient
- Stop any current drugs that are not indicated
- Prescribe new drugs that have a clear indication
- If possible, avoid drugs that have known deleterious effects in elderly patients, and recommend dosage reduction when appropriate
- Use the recommended dosages for elderly patients
- Use simple drug regimens and appropriate administration systems
- Consider using once daily or once weekly formulations and using fixed dose combinations when possible
- Consider non-pharmacological treatments if appropriate
- Limit the number of people prescribing for each patient if possible
- Where possible, avoid treating adverse drug reactions with further drugs

Therefore, sharing medication management responsibilities with other health care professionals seems an approach worth considering. Furthermore, use of healthcare information technology (HIT) to promote safe medication prescribing seems inevitable.

**SHARING RESPONSIBILITIES**

When it comes to improving prescribing, pharmacists have for years been the driving force behind interventions aimed at reduction of medication errors and ADEs in various patient populations and settings. 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 availability of clinical pharmacists who provide medication reconciliation at admission and on discharge, conduct medication reviews, monitor pharmacotherapy during hospital stay and after discharge, provide pharmacotherapy education for physicians and nurses, and write guidelines and protocols for safe medication use on the wards (active approach). As members of a multidisciplinary team, clinical pharmacists often engage their expertise in identifying medication-related problems by conducting comprehensive medication reviews and individualizing pharmacotherapy according to patients’ needs.

**HEALTH INFORMATION TECHNOLOGY**

CPOE with an integrated clinical decision support system (CPOE-CDSS) is a promising intervention which has been shown to reduce medication errors and, in some instances, ADEs. A basic and most common CDSS type currently operating in Dutch hospitals is the Dutch drug database ‘G standard’. This database contains safety information on all drugs registered in the Netherlands and generates drug-drug interactions to alert the prescriber when co-prescribing certain drugs is likely to result in ADEs. Another common CDSS type is the clinical decision support module, which is a computerized system that provides real-time assistance to the prescriber while he is writing a prescription.
interactions and duplicate orders alerts, and general dosing advice while prescribing.\textsuperscript{50}

**DEVELOPING AND IMPLEMENTING INTERVENTION STRATEGIES**

Although results from published studies can provide clues how to improve prescribing for older inpatients, each hospital needs to identify and evaluate its own weak spots in this process before choosing an intervention strategy. Therefore, the 1\textsuperscript{st} step should be a measurement on how safe this process is in daily practice.

As a 2\textsuperscript{nd} step, local ADE data, should be analyzed with professionals involved in the medication prescribing process to determine which medication error safety nets are lacking or at risk of failure, and to develop interventions.\textsuperscript{51} Some safety nets are system-based (e.g., availability of medication guidelines and a CPOE-CDSS) and some rely on people (e.g., pharmacotherapy knowledge of physicians, daily supervision by attending physicians). In an ideal world each safety net would be intact. In reality, however, they are more like slices of Swiss cheese, having many holes (Figure 2). These holes represent weak spots arising from either unsafe actions by individuals (active failures) and/or failures on organizational level (latent conditions).\textsuperscript{52}

**Figure 2**  
The Swiss Cheese model for the process of prescribing

![The Swiss Cheese model for the process of prescribing](image)

Adapted from Reason J. West J Med. 2000; 172(6): 393–396\textsuperscript{52}

Once an intervention strategy is developed, as a 3\textsuperscript{rd} step barriers in implementing this strategy in daily practice should be listed, and an approach to tackle these barriers should be set. Finally, as a 4\textsuperscript{th} step the effect of the intervention strategy implemented should be evaluated and future directives should be determined. This 4-step approach is the framework of this thesis.
OBJECTIVES OF THIS THESIS
The objective of this thesis is first to determine medication safety in older inpatients by measuring ADEs and by applying 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. The scope of medication safety primarily highlighted in this thesis is medication prescribing.

OUTLINE OF THIS THESIS
This thesis consists of the following parts.

PART 2: ADVERSE DRUG EVENTS IN OLDER INPATIENTS
So far, no ideal method for measuring medication safety has been defined. Therefore, when prompted with a need to measure ADEs in older inpatients, in a setting where such measurement has not been conducted before, we chosen PCR as the basis because of its high sensitivity and specificity, and an adapted IHI ADE trigger-tool was applied as an aid during the review (not for patient pre-selection). Also, we applied broad and internationally accepted definitions and tools to assess causality and severity of ADEs to gain a detailed and structured measurement. This strategy was used to identify ADEs in older inpatients in three Dutch hospitals. Preventable ADEs are discussed in more detail in Chapter 2.1 and ADE recognition by medical teams in Chapter 2.2.

PART 3: QUALITY OF CARE IN OLDER INPATIENTS
In 2001, the ACOVE (Assessing Care Of Vulnerable Elders) QIs were developed in the US to measure the overall quality of care of community-dwelling vulnerable older patients. Chapter 3.1 describes adaptation of the ACOVE QIs set to measure the quality of in-hospital pharmaceutical care of Dutch older patients (ACOVE-NL). The ACOVE-NL QIs set was judged on face and content validity, the feasibility of implementation, and inter-rater reliability. Subsequently, ACOVE-NL QIs were used to measure medication safety in older inpatients and to define the association of this QI set with hospital readmissions, and mortality (Chapter 3.2).

PART 4: CONCEPTUALIZING AND DESIGNING WARD-ORIENTED PHARMACY
A pilot study on the Intensive Care Unit (ICU) was conducted to examine whether the clinical pharmacy practice, not common in Dutch hospital setting, can be equally effective in reducing preventable ADEs and medication errors as compared to settings in which this practice is well established (Chapter 4.1). Based on the experiences gained on the ICU, we tailored and further refined the clinical pharmacy practice model to the Dutch hospital setting, i.e., “ward-oriented” pharmacy. Furthermore, aspects of ADE measurement were critically reviewed. In Chapter 4.2 the protocol of Ward-oriented pharmacy In Newly admitted Geriatric Seniors (WINGS) study is presented in which implementation strategy including ward-oriented pharmacy concept has been outlined.

PART 5: MULTIFACETED INTERVENTION STRATEGIES
Few published studies on prescribing interventions for older inpatients have used ADEs as patient outcome measure to evaluate the effects of interventions implemented. Furthermore, most studies implemented single intervention and none
have addressed ADE recognition by medical teams. Therefore, a multicentre, interrupted time series study was conducted to investigate the effect of a multifaceted intervention strategy (MFIS) on preventable ADEs and on ADE recognition in older inpatients (Chapter 5.1).

Medication safety interventions are often complex to implement because they frequently require not only major changes in workflows but also in safety culture. Therefore, knowledge on the sustainability of such interventions in daily practice (once the interventions are no longer the responsibility of a research team) is of great importance to be able to maintain the improvements gained. Yet, information on this topic is limited. In Chapter 5.2 a study on the short- and long-term effects of an MFIS on medication administration errors in nursing home residents with swallowing difficulties is presented.

PART 6: GENERAL DISCUSSION
In Part 6 the results of the different studies are discussed and recommendations for clinical practice and further research on medication safety in older inpatients are provided.
REFERENCES


