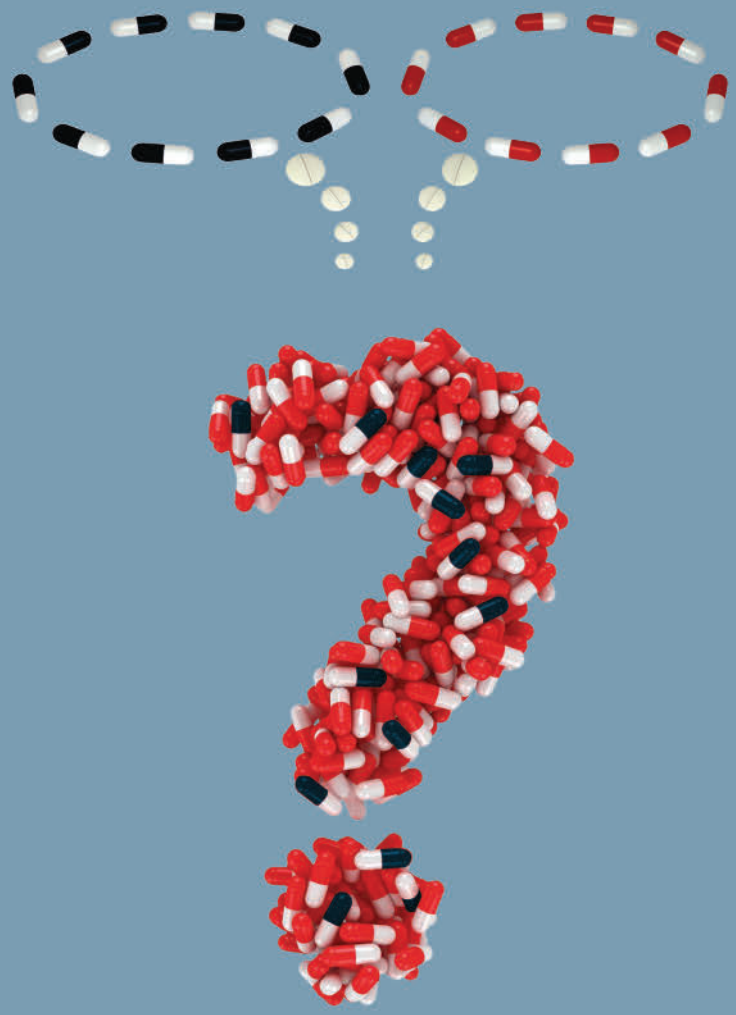
MEDICATION RECONCILIATION

Risk Factors and Ways to Improve Efficiency



Marieke M. Ebbens

MEDICATION RECONCILIATION:
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Risk Factors and Ways to Improve Efficiency

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CHAPTER

1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Information on patient medication use is prone to errors in transfer of care situations, due to the lack of an integrated nationwide electronic medication record. Patients can have different prescribers from different hospitals and his/her general practitioner. In addition, they may collect the medication at different pharmacies having multiple pharmacy records. Furthermore, patients sometimes change the dosage without consulting the prescriber or stop taking prescribed medication at all. Therefore, without an integrated system the patient him/herself is the best source of actual medication use. However, in acute hospitalisations communication with the patient is not always possible, adding further to the risk of medication transfer errors.

Medication transfer errors are defined as unintentional discrepancies between medication used at home and medication prescribed during admission in the hospital or at hospital discharge. At admission, 27-54% of patients had at least one medication transfer error. Of those medication errors, 11-59% were clinically important.[1] At hospital discharge, a median of 60% of patients had a medication transfer error at discharge, with a wide range of 20-87%.[2] A medication transfer error can have serious consequences. For example, missing treatment for existing medical conditions can cause serious medical complications and unintentional duplicate treatment can cause serious side effects.

Medication reconciliation

Unintentional medication transfer errors can be reduced by medication reconciliation. Medication reconciliation is the process of creating the most accurate list of all medications a patient takes - including drug name, dosage, frequency and administration route.[3] The resulting medication list is also referred to as the Best Possible Medication History (BPMH). By comparing the BPMH to the physician's prescriptions at admission, transfer or discharge, medication discrepancies can be discovered. Medication discrepancies can be intentional in case drug therapy is changed in response to changes in medical conditions. When medication discrepancies are unintentional, these are defined as medication transfer errors.

Medication discrepancies can be reduced by 42 - 45% by performing medication reconciliation.[4, 5] After reconciling all medication and creating the BPMH, all discrepancies between the physician's prescriptions and the BPMH are discussed with the physician to establish intentional and unintentional discrepancies. Unintentional medication discrepancies are resolved and medication transfer errors are prevented. Medication reconciliation has been shown to be cost effective in reducing medication transfer errors that could have caused adverse effects.[6]

In the Netherlands it is common to use the community pharmacy dispensing record as a primary source of home medication when a patient is admitted to the hospital. Healthcare professionals can consult this nationwide medication record system (NMRS) electronically. The patient has to give formal consent to the community pharmacy for

sharing this information. The NMRS overview can be complemented using information from the hospital electronic patient record. A patient interview is conducted to discuss all medications on the overview and ask if any additional medication is used. The patient interview to verify the medication use is necessary because the NMRS overview is accurate in less than 20% of the patients.[7] Combining the information from the NMRS, hospital record and patient interview results in the BPMH. (Figure 1)

Medication reconciliation in hospitals started as part of the nurse or physician admission procedure. However, pharmacy-led medication reconciliation is proven to be more effective in reducing medication transfer errors than medication reconciliation performed by other healthcare professionals.[8] This can be explained by the fact that pharmacy professionals can fully focus on medication in a medication reconciliation interview, while nurses and physicians have a broader scope. However, implementation of pharmacy-led medication reconciliation in clinical practice is difficult. Introducing pharmacy professionals in the admission and discharge routing to perform medication reconciliation, requires adjustments in procedures. Furthermore, medication reconciliation can be time consuming, taking a median of 50 minutes at admission and discharge, therefore increasing healthcare costs.[9] For every 10,000 clinical admissions, 8,300 hours are needed for medication reconciliation. With around 1,820 working hours a year, this takes 4.5 full time pharmacy technicians per 10,000 admissions per year. In the Netherlands in 2017 there were 1.6 million clinical admissions in hospitals.[10] Thus, it would take 726 full time pharmacy technicians to perform medication reconciliation in all clinical admissions in the Netherlands.

Due to rising healthcare costs, hospitals are required to deliver healthcare for the same yearly budget the coming years. Opportunities to expand the number of pharmacy technicians in order to perform medication reconciliation are limited by these budgetary constraints. In addition, there is a growing shortage of pharmacy technicians. With the knowledge that medication reconciliation prevents medication errors, and the limited resources available, more efficient ways to perform medication reconciliation are needed.

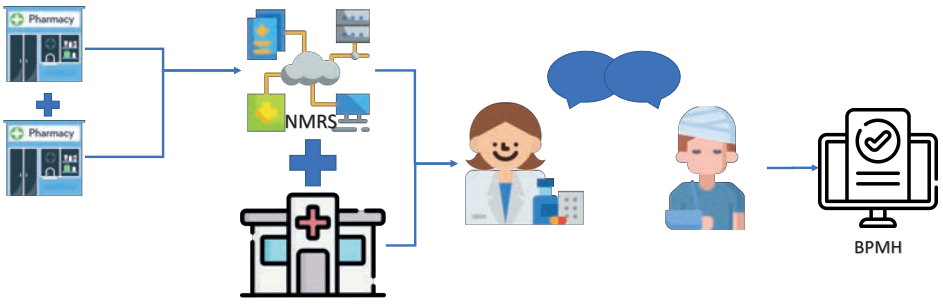

Figure 1 Medication reconciliation. Dispensing information from different pharmacies is combined in the nationwide medication record system (NMRS).Together with the information from the hospital record and patient interview, this results in an Best Possible Medication History (BPMH).

Improving efficiency in medication reconciliation may be accomplished in various ways. First, the focus on medication reconciliation could be shifted to patients at high risk for medication discrepancies. Medication reconciliation for high risk patients can be performed by pharmacy professionals, whereas medication reconciliation in patients with low risk can be performed by other healthcare professionals. Second, electronic tools can be introduced to increase efficiency in the medication reconciliation process and simplify the process, enabling other healthcare professionals to perform medication reconciliation. Third, medication reconciliation can be performed electronically in a patient portal by patients themselves, i.e. empowering the patient with regard to their medication use. These three approaches to improve efficiency are discussed in more detail below.

Focus on high risk patients

The efficiency of medication reconciliation may be improved by focusing pharmacist led medication verification on high risk patients. Hias et al. reviewed the literature to assess risk factors for discrepancies in preadmission medication.[11] The number of preadmission drugs was identified as a risk factor in 20 of 35 included studies. In 13 out of 15 studies, the number of preadmission drugs was found to be an independent risk factor. Age was an independent risk factor in 4 out of 4 studies. Another 14 variables were identified as potential independent risk factor in at least one study. However, validated risk prediction models to identify patients at high-risk for medication errors are lacking. Yet, such a model could help to prioritize patients to receive pharmacy-led medication reconciliation.

Medication reconciliation with electronic tools

Another way to improve the efficiency of the process of medication reconciliation may be found in the application of electronic tools. Mequerditchian et al. concluded in a time-and-motion study that standardization of the medication reconciliation process and use of electronic tools could improve efficiency.[12] Furthermore, medication reconciliation supported by an electronic tool can minimize the incidence of unintended discrepancies.[5] In the meta-analysis by Mekonnen et al., electronic tools were used by healthcare professionals to facilitate the medication reconciliation process and these tools reduced the number of unintended medication discrepancies. Furthermore, a meta-analysis by Wang et al. also showed that electronic medication reconciliation reduced the incidence of unintended medication discrepancies.[13] The next step would be to empower the patient to perform medication reconciliation with an electronic tool, and save time and thus costs from healthcare professionals.

Patient involvement in medication reconciliation

In the first studies on patient involvement in medication reconciliation patients were given an empty list and were asked to fill this with the medications they used. This often resulted in incomplete medication lists.[14, 15] With the possibility of electronically exchanging

information, it became possible to present a medication list from (for example) a hospital record and let the patient correct any inconsistencies. When patients were presented with a medication list and asked to adjust and supplement this list, the quality of the generated medication list generally improved.[16-19] Marien et al. also investigated patient satisfaction with patient portal medication reconciliation. They found that patient involvement in medication reconciliation improves the communication between patients and their healthcare professionals about their medication. Also, patients are generally satisfied with using a patient portal to complete their medication list.[16] In the pilot study of Heyworth et al., 10 patients were interviewed on their experiences with 'Secure Messaging for Medication Reconciliation Tool' (SMMRT) within a patient web portal. All patients found the SMMRT easy to use, although a third to half of the patients indicated some challenges navigating the web portal or experienced initial technical difficulties. Nine out of ten patients would use the SMMRT again.[17] So the first experiences with patient portal medication reconciliation are positive, but there are no studies known to compare the patient portal medication reconciliation to the current gold standard of pharmacy led medication reconciliation. Furthermore, all current studies use different tools and information on the best tool for patient portal medication reconciliation is lacking.

Objectives of this thesis

The first aim of this thesis is to identify risk factors for medication transfer errors. A risk prediction model will be constructed and validated to be able to select patients at high risk for medication transfer errors.

The secondary aim is to study if allocating patients to different medication reconciliation methods based on risk factors is safe.

Finally, patient portal medication reconciliation is investigated to establish if this is non-inferior to pharmacy-led medication reconciliation.

OUTLINE OF THE THESIS

Part 1

The first part of this thesis focuses on risk factors of medication errors.

In **chapter two,** scientific literature is systematically reviewed to assess risk factors of medication errors in transitions of care. This review differentiates between intentional and unintentional medication discrepancies to determine medication transfer errors, in contrast to existing reviews . Studies were included that identified risk factors of medication errors, defined as unintentional medication discrepancies on hospital admission or discharge.

Chapter three focuses on identification of risk factors of medication discrepancies in acutely admitted patients in the emergency department. In **chapter four,** risk factors of medication transfer errors at admission in pre-operatively screened patients were identified and used to construct a risk prediction model.

The validation of this risk prediction model within another patient population is described in **chapter five.**

Part 2

The second part of this thesis describes studies of methods to perform medication reconciliation in a more efficient way.

In **chapter six,** differentiating medication reconciliation by different healthcare professionals based on the number of medications in the preoperative setting is studied. In patients using two or more medications, pharmacy technicians performed medication reconciliation. In all other patients, anaesthesiologists performed the medication reconciliation during a routine visit.

Chapter seven describes the prevalence of medication transfer errors in ambulatory nephrology patients. In this study, the Medical Dashboard is used to integrate the NMRS overview with the medication from the hospital record, which enables a medical attendant to perform medication reconciliation.

In **chapter eight,** the non-inferiority of performing medication reconciliation by patients using a patient portal application compared to the current standard of pharmacy technicians performing the medication reconciliation is studied in a randomized controlled trial.

The general discussion, **chapter nine**, provides an overview of all findings in this thesis. Furthermore, the results are discussed together with implications for clinical practice and recommendations for future research.

REFERENCES

1. Tam, V.C., et al., *Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review.* CMAJ, 2005. **173**(5): p. 510-515.
2. Michaelsen, M.H., et al., *Medication Reconciliation at Discharge from Hospital: A Systematic Review of the Quantitative Literature.* Pharmacy, 2015. **3**(2): p. 53-71.
3. Institute for Healthcare Improvement, *Reconcile medications at all transition points.* 2021 cited 2021 5 May;
4. Cheema, E., et al., *The impact of pharmacists-led medicines reconciliation on healthcare outcomes in secondary care: A systematic review and meta-analysis of randomized controlled trials.* PLoS One, 2018. **13**(3): p. e0193510.
5. Mekonnen, A.B., et al., *Impact of electronic medication reconciliation interventions on medication discrepancies at hospital transitions: a systematic review and meta-analysis.* BMC Med Inform. Decis Mak, 2016. **16**: p. 112.
6. Karnon, J., F. Campbell, and C. Czoski-Murray, *Model-based cost-effectiveness analysis of interventions aimed at preventing medication error at hospital admission (medicines reconciliation).* J Eval Clin Pract, 2009. **15**(2): p. 299-306.
7. Uitvlugt, E.B., et al., *Validity of a nationwide medication record system in the Netherlands.* Int J Clin Pharm, 2019. **41**(3): p. 687-690.
8. Mekonnen, A.B., A.J. McLachlan, and J.A. Brien, *Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis.* J Clin Pharm Ther, 2016. **41**(2): p. 128-144.
9. Hammad, E.A., et al., *Pharmacy led medicine reconciliation at hospital: A systematic review of effects and costs.* Res Social Adm Pharm, 2017. **13**(2): p. 300-312.
10. Centraal Bureau voor de Statistiek, *Ziekenhuisopnamen en patiënten 2017*. 2017 cited 2020 10 Nov;
11. Hias, J., et al., *Predictors for unintentional medication reconciliation discrepancies in preadmission medication: a systematic review.* Eur J Clin Pharmacol, 2017. **73**(11): p. 1355-1377.
12. Meguerditchian, A.N., et al., *Medication reconciliation at admission and discharge: a time and motion study.* BMC Health Serv Res, 2013. **13**: p. 485.
13. Wang, H.M., et al., *Electronic medication reconciliation in hospitals: a systematic review and meta-analysis.* European Journal of Hospital Pharmacy-Science and Practice, 2018. **25**(5): p. 245-250.
14. Lee, K.P., et al., *Predictors of completeness of patients' self-reported personal medication lists and discrepancies with clinic medication lists.* Ann Pharmacother, 2014. **48**(2): p. 168-77.
15. Witting, M.D., et al., *Emergency department medication history taking: current inefficiency and potential for a self-administered form.* J Emerg Med, 2013. **45**(1): p. 105-10.
16. Marien, S., et al., *A web application to involve patients in the medication reconciliation process: a user-centered usability and usefulness study.* J Am Med Inform Assoc, 2018. **25**(11): p. 1488-1500.
17. Heyworth, L., et al., *Engaging patients in medication reconciliation via a patient portal following hospital discharge.* J Am Med Inform Assoc, 2014. **21**(e1): p. e157-62.

18. Kripalani, S., et al., *Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial.* Ann Intern Med, 2012. **157**(1): p. 1-10.

19. Prey, J.E., et al., *Engaging hospital patients in the medication reconciliation process using tablet computers.* J Am Med Inform Assoc, 2018. **25**(11): p. 1460-1469.

PART I

RISK FACTORS OF MEDICATION ERRORS

CHAPTER

2

INDEPENDENT RISK FACTORS OF MEDICATION ERRORS IN HOSPITAL ADMISSION AND DISCHARGE; A SYSTEMATIC REVIEW

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In preparation

ABSTRACT

Background

Patients at transitions of care are known to have a high risk of medication errors. In this review a comprehensive overview of independent risk factors associated with these medication errors is given.

Purpose

Identifying independent risk factors of medication transfer errors occurring at hospital admission and discharge.

Data Sources

A systematic search in the medical databases PubMed, EMBASE, Web of Science, and Cochrane library was performed, we included papers published from inception to November 9th 2020.

Study Selection

Titles and abstracts of the articles retrieved by the search were assessed on three topics: medication transfer errors defined as non-intentional discrepancies, risk factors, and hospital admission and discharge.

Data Extraction

The following data from the included studies were extracted: first author, year of publication, study design, setting, transition stage (admission, discharge, or both), inclusion and exclusion criteria, sample size, medication reconciliation method, primary outcome, definition of medication error, risk factors, statistical analysis, and quality of the study. The number of studies in which each independent risk factor of medication transfer errors was identified, was counted. The top five independent risk factors is reported.

Data Synthesis

Number of medications is the most frequently reported independent risk factor of medication transfer errors , followed by age, type of medication, information sources for medication reconciliation, and comorbidity at admission. At discharge number of medications is followed by physician level, medication changes during hospitalisation, hospital ward, and residential situation.

Limitations

Publication bias could have led to overestimation of associations.

Conclusions

Number of medications is the most frequently identified independent risk factor of medication transfer errors at hospital admission and discharge.

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INTRODUCTION

Medication errors at admission occur in up to 67% of patients.[1] A median of 45% of patients have at least one medication error at discharge, and patients experience on average 1.2-5.3 discrepancies when leaving the hospital.[2, 3] At admission between 12 and 19% of the medication errors are potentially harmful, which can lead to patient harm and/or extended hospital admission.[4-6] At discharge 31% of the patients had at least one clinically relevant discharge medication error.[7] Thus, patients at transitions of care are at high risk of medication errors, because information needs to be transferred between different health care institutions.

Medication reconciliation (MR) has proven to reduce the occurrence of medication errors.[3, 8-13] MR is the process in which the best possible medication history (BPMH) of a patient is constructed by combining multiple information sources such as a medication overview from a community pharmacy, general practitioner, and hospital electronic patient record with a (semi)structured patient interview. Subsequently, the BPMH is compared to the admission or discharge medication orders and any discrepancy is discussed with the responsible physician to establish if medication changes were made intentionally or not. Since this process is time consuming and requires the attention of several health care professionals, it is a very costly process[14].

Medication reconciliation can be more efficient if only patients at high risk of medication errors are included in the process. Although medication errors occur in up to 67% of the patients, the remaining one-third of the patients do not have medication errors.[1, 15] Therefore, if risk factors can be identified of medication errors at transitions of care, medication reconciliation can be targeted to patients at risk rendering the medication reconciliation process more efficient.

For identification of risk factors different strategies are used. Often single variables are tested for significant influence in univariable analysis. If these are statistically significant they are considered dependent risk factors. To identify independent risk factors multivariable statistical analysis is needed to adjust for potential confounders.

Several studies have been performed to determine which patients are at risk of medication errors. A review by Hias et al. identified 16 independent risk factors of preadmission medication related discrepancies.[16] However, the definition of medication discrepancy of the included studies differed widely and often included intentional discrepancies, which should not be regarded as a medication transfer error.[16] Furthermore, only 23 of the 35 included studies adjusted for confounders by performing multivariable analyses.[16] A review by Suggett et al. identified the ten most frequently reported risk factors associated with medication related problems during hospital admission that may lead to a hospital pharmaceutical intervention.[17] However, they did not distinguish between dependent and independent risk factors in creating the top ten of risk factors identified in literature. Systematic reviews on independent risk factors of medications errors at both hospital admission and discharge have not been performed. Therefore,

in this systematic literature review we aimed at identifying independent risk factors of medication transfer errors occurring at hospital admission and discharge.

METHODS

Data source and search

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[18] The protocol - written according to the PRISMA-p checklist – was registered in the international prospective register of systematic reviews Prospero registration number CRD42017057593.

A systematic search in the medical databases PubMed, EMBASE, Web of Science, and Cochrane library was performed from inception to November 9th 2020. The search consisted of three topics: medication errors, risk factors, and transitions of care. All databases were searched taking into account the terminological and technical differences between these databases. Various synonyms and related terms for all three topics were used. After a first screening of 100 articles the search was refined by excluding the terms rehospitalisation, potentially inappropriate medications, and drug-drug interactions. Meeting abstracts were also excluded. Only studies with an abstract available in English were included, there was no exclusion criterion on language of the full text. The Pubmed search strategy is added in Appendix 1. Reference lists of reviews identified by the search were screened for additional articles that could potentially be included.

Study selection

Titles and abstracts of the articles retrieved by the search were assessed on three topics: medication errors, independent risk factors and hospital admission and discharge. Only original studies were included in the systematic review with no restrictions on study design. Reviews were only used to scan the reference lists for potentially eligible studies not detected in the initially literature searches. Studies in which no transition of care situation at hospital admission or discharge was described or no independent risk factors were analysed were excluded. We applied a strict definition of medication transfer errors and only studies complying to that definition were included.

Medication transfer errors at admission were defined as non-intentional medication discrepancies when comparing the BPMH with the medication prescribed in the medical record of the patient when admitted to hospital.

Medication transfer errors at discharge were defined as non-intentional medication discrepancies between the medication in use after discharge and the discharge letter.

Whether a medication discrepancy was intentional or unintentional could be determined by discussing with the prescribing physician, or by reviewing available documentation. In order to be included, the article needed to mention explicitly which type of discrepancies were studied.

Two authors (ME and SL) screened titles independent from each other. There were three selection options: include in the review, exclude, or read full text to assess eligibility. Disagreements on the selection by title and abstract were resolved through discussion with a third author (KG). The full text of the selected abstracts was subsequently assessed on medication errors, risk factors and transitions of care. The same two authors screened the full text articles independent from each other. Again, disagreement on the selection of the full text references was resolved through discussion with a third author (KG).

Data extraction and outcomes

The following data from the included studies were extracted: first author, year of publication, study design, setting, transition stage (admission, discharge, or both), inclusion and exclusion criteria, sample size, medication reconciliation method, primary outcome, definition of medication error, risk factors, statistical analysis, and quality of the study. To prevent bias in the reported risk factors in the studies, from every study not only the statistically significant risk factors were included in the analysis but also which risk factors were analysed. For medication transfer errors at admission only risk factors that were already present at the moment of admission were included. The same method was applied for risk factors of medication transfer errors at discharge.

Quality assessment

For the quality of the study the Newcastle-Ottawa quality assessment scale (NOS) for non-randomized studies was used to assess the quality of the included studies. One of the authors (ME) used the NOS scale to establish the quality of the included studies.[19] Studies with a NOS quality score below 3 were excluded.

The primary outcomes of this systematic review were independent risk factors (significantly associated in multivariable analysis) of medication transfer errors at hospital admission and discharge. The independent risk factors were ranked by the number of studies they were identified by.

RESULTS

The literature search resulted in 1450 unique references. After screening, 44 studies were included in the review (Figure 1).

Characteristics of reviewed studies

Descriptive data from the 44 included studies are presented in Table 1 for admission and Table 2 for discharge.

Most studies were observational cohort studies in a limited number of wards within one hospital. 72% (29/44)[4, 6, 15, 20-45] of the studies focused on medication transfer errors at admission, twenty percent (9/44)[46-54] focused on medication errors at discharge and nineteen percent (6/44)[7, 55-59] looked at both admission and discharge. Some studies were

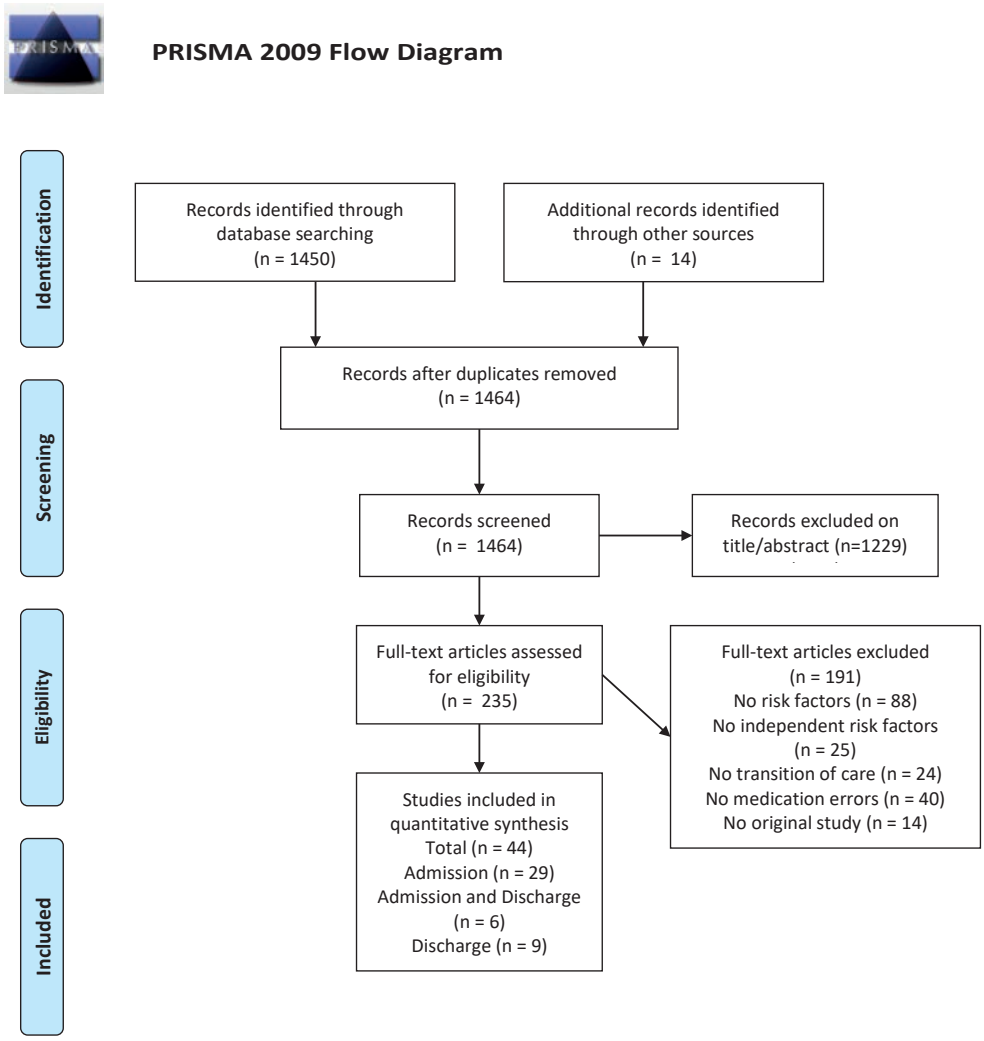

Figure 1. Flow chart

performed in one or two wards of the hospital, while others included for example all acutely admitted or all elective surgery patients regardless of medical specialty. Inclusion criteria differed with respect to the patients' age, duration of the admission and number of medicines in use. The sample size varied from 83[50] to 1884[20] patients. The NOS quality score of the included studies varied between 3 and 6 (Table 1 and 2).

The percentage of patients with at least one medication error at admission varied from 3.8%[55] to 81.9%[25]. At discharge the percentage of patients with at least one medication error varied from 1.6%[55] to 88.9%[49].

Independent risk factors

The statistics used in the different studies varied, univariable and multivariable logistic regression were most often used to identify risk factors. At admission 35 studies[4, 6, 7, 15, 20-45, 55-59] determined independent risk factors, at discharge 15 studies[7, 46-59] determined independent risk factors. The top 5 of independent risk factors of medication transfer errors at admission are described below. In appendix 2 all independent risk factors of medication errors at admission are presented.

Top 5 independent risk factors of medication transfer errors at admission

1. Number of medications

At admission 25 out of 34 studies[7, 20, 21, 23-25, 27-33, 35-40, 43, 45, 58, 59] analysed number of medications. From these 24 studies[7, 20, 21, 24, 25, 27-33, 35-40, 43, 45, 58, 59] identified the number of medications as a significant independent risk factor. Fourteen studies analysed the number of medications in categories and found a range of 3 or more medications till 16 or more medications in use to increase the risk of medication transfer errors. Only one study found using > 8 medications not to be a significant risk factor in the multivariate analysis.[23] The other ten studies analysed the number of medications as a continuous variable, nine studies reported adjusted odds ratios between 1.10 and 1.47 for each additional medication, one study reported an incidence rate ratio (IRR) of 1.07. The reported adjusted odds ratios (aOR) with 95% confidence intervals (95%-CI) are shown in Figure 2.

2. Age

Age is analysed as a potential risk factor in 17 studies[4, 6, 7, 22, 26, 32-34, 36-39, 41, 43, 57-59] of which 10 (59%)[4, 6, 7, 26, 34, 38, 39, 41, 43, 59] showed it to be an independent risk factor. One study found older patients to be at lower risk than younger patients[34], while in all other studies older patients were at higher risk. Two studies reported adjusted odds ratios of 1.01-1.02 per increasing year of age.[43, 59] Two other studies that analysed age as a continuous variable reported only a significant p-value[41] or an IRR of 1.84[7]. One study reported an aOR of 1.16 per every 5 year increasing age.[6] Two studies reported adjusted odds ratios of 2.7 for patients ≥ 65 years[38, 39], and one study reported an aOR of 2.17 for patients ≥ 65 years[4]. One study found patients of 60 years or older to have a higher risk of medication transfer errors.[26]

3. Type of medication

In five out of the seven studies in which the type of medication was analysed, the type of medication is a significant independent risk factor. In one study taking any high-risk drug (based on the Institute for Safe Medication Practices (ISMP) and the North Carolina Narrow Therapeutic Index (NTI) classification) was found to be a risk factor with an aOR of 76[6], in two studies antidiabetics were associated with an aOR of 2.6[38, 39], in one study chronic respiratory medication was associated with an adjusted risk ratio of 1.5[27]

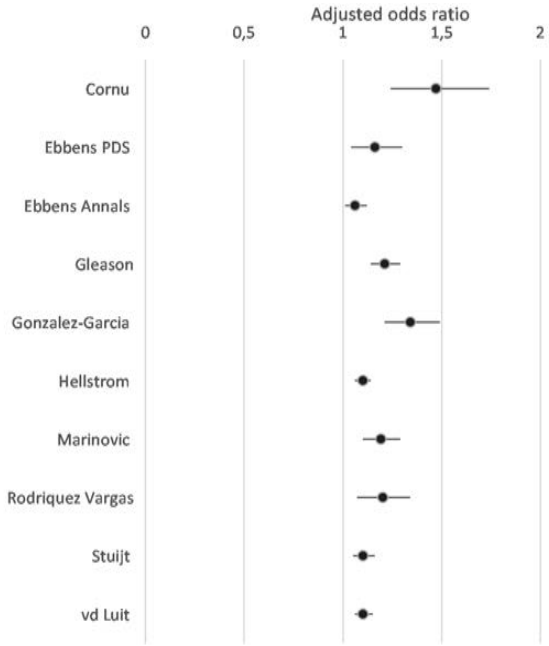

Figure 2. Adjusted odds ratios of number of medications with 95% confidence interval of different studies.

and the last study identified baclofen as a risk factor with an aOR of 2.2[22]. Taking into account that antidiabetic drugs are part of the high-risk drugs, three studies showed that antidiabetic drugs were associated with an increase of the risk of medication transfer errors at admission.

4. Information sources for medication reconciliation

In four out of six studies in which using different information sources for medication reconciliation was studied it was found to be a significant risk factor. The number of information sources used for medication reconciliation was found to be a risk factor with an aOR of 1.78.[25] An IT-guided checklist was found to significantly reduce the risk of medication transfer errors.[34] Another study found the use of a computerized physician order entry system to reduce the risk of medication transfer errors with an aOR of 0.43.[40] Presenting a medication list upon admission was found to reduce the risk of medication errors with an aOR of 0.35.[4] However, two studies found the availability of a medication list or medication bag not to be a significant risk factor of medication errors at admission.[7, 38]

5. Comorbidity

Four out of seven studies which analysed different comorbidities found this to be a significant risk factor. Different comorbidities were found to be a risk factor of medication

errors at admission. Respiratory disease with an aOR of 4.25[28], having asthma with an aOR of 6.37[44], thyroid disease with an aOR of 1.79,cardiovascular disease with an aOR of 1.80[57] and having type 1 diabetes mellitus with an aOR of 1.72[56]. However, different comorbidities were not found to be a significant risk factor in three other studies.[15, 22, 55]

Table 1. Characteristics of reviewed studies at admission

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Audurier 2020	Single center prospective observational study	Internal medicine department	Admission	> 18 years > 24 hour admission	1884	BPMH based on at least 3 information sources of which structured patient or family member interview is one.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
Patients with at least one medication error related to medication reconciliation	In agreement with the prescriber when an unintended medication discrepancy was detected it was considered an medication error.	31.1%	Age >75 years, gender, cardiovascular disease, high blood pressure, dyslipidemia, thyroid disease, neurologic diseases, psychiatric disease, chronic diseases > 3, number of treatments > 7, admission from emergency department, admission during night or weekend, living area,	Univariable: Age > 75 years OR 1.7 (95%-CI 1.2-2.2), gender (female) OR 1.4 (95%-CI 1.1-2.0) cardiovascular disease OR 1.5 (95%-CI 1.1-2.1), high blood pressure OR 1.5 (95%-CI 1.1-2.0), chronic disease > 3 OR 1.6 ((95%-CI 1.2-2.1), number of treatments > 7 OR 1.7 (95%-CI 1.2-2.1), emergency admission OR 2.0. (95%-CI 1.4-2.7), night/weekend admission OR 1.8 (95%-CI 1.4-2.5), living area home vs institution OR 0.6 (95%-CI 0.4-0.9). Multivariable Gender (female) OR 1.4 (95%-CI 1.0-1.9. Number of treatments > 7 OR 1.7 (95%-CI 1.3-2.3), emergency admission OR 1.6 (95%-CI 1.1-2.3), night/weekend admission OR 1.5 (95%-CI 1.1-2.1)	Univariable and multivariable logistic regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Barbier 2020	Single center prospective observational study	Geriatric short stay department	Admission	Alive 72 hours after admission	658	Medication reconciliation based on WHO guidelines
Blaine, 2020	Prospective, dual-center cohort study	Children with medical complexity	Admission	Children with medical complexity	1233	Resident physicians obtained patient medical history including review of home medications.
Breuker 2016	Single center prospective observational study	Endocrinology, Diabetology and Nutrition department	Admission and Discharge	> 18 years >24 hour admission	904	Medication reconciliation using patient records and structured patient interview

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
Patients with at least one unintentional medication discrepancy at admission	Medication discrepancies were discussed with the prescriber who determined if it was intentional or unintentional.	24.5%	Age, autonomy at home, number of drugs, admission reason, admission type, medical specialty of admission, ATC class drugs	Univariable: Admission reason (electrolyte disorder or digestive problems), > 9 number of drugs, ATC class H or S. Multivariable: Admission reason electrolyte disorder OR 3.2 (95%-CI 1.31–7.94), > 9 number of drugs OR 1.6 (95%-CI 1.13–2.33)	Univariable and multivariable logistic regression	4
Presence of medication order error at admission	Medication order errors were identified by comparing the medication orders to the prior documentation in the electronic medical record.	6.1%	Gender, age at admission, payor (public, private, and other), race, type of chronic condition, number of complex chronic conditions, assistance with medical technology, number of medications, type of medication	Univariable: > 6 years OR 2.7 (95%-CI 1.1-6.7), > 10 medications OR 2.1 (95%-CI 1.3-3.5),>6 therapeutic categories OR 1.8 (95%-CI 1.1-3.1), >2 complex chronic conditions OR 2.1 (95%-CI 1.0-4.3), chronic condition assisted with medical technology OR 2.0 (95% CI 1.1-3.8), using baclofen p< 0.001, using clobazam p<0.05. Multivariable: using baclofen aOR 2.2 (95% CI 1.2-3.8)	Chi-square test, Fisher exact test, multivariabel generalized linear mixed model to correct for the hospital	4
Number of patients with medication (transfer) errors.	Medication errors are defined as unintended discrepancies corrected by the physician.	3.8%	Model 1: Having diabetes Model 2: having diabetes, admission period, number of prescription lines Model 3: model 2 + age and sex.	Univariable diabetes OR 1.79 (1.15-2.80) Multivariable no significance	Univariable and multivariable logistic regression	3

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Breuker 2017 DM	Single center prospective observational study	Diabetology department of university hospital	Admission and Discharge	> 18 years >24 hour admission	671	Medication reconciliation using patient records and structured patient interview
Breuker 2017 JPS	Single center prospective observational study	Endocrinology, Diabetology and Nutrition department	Admission and Discharge	>18 years	904	Medication reconciliation using patient records and structured patient interview
Chung 2019	Single center prospective observational study	Cardiology department of a university teaching hospital	Admission	>24 hour admission	100	The BPMH was compiled from various sources of information including patient/family interview.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
Patients with at least one medication error.	Medication errors are defined as unintended discrepancies corrected by the physician.	29.4%	Age, number of treatment lines in prescription, type of diabetes.	Type 1 diabetes OR 1.72 (95% ci 1.02-2.94)	Multivariable logistic regression	3
Patients with at least one medication error.	Medication errors are defined as unintended discrepancies corrected by the physician.	29.4%	Age, sex, BMI, admission reason, associated chronic diseases, number of chronic diseases, type of admission, time of admission, length of stay, living area, number of medications	Univariable: Age OR 1.02 (95% CI 1.01-1.03), number of chronic diseases p<0.001, admitted for diabetic foot p=0.02, emergency admission p=0.01, number of medications p<0.001. Multivariable adjusted for number of treatments: Thyroid disease aOR 1.79 (95%CI 1.12-2.86), Cardiovascular disease aOR 1.80 (1.17-2.78).	Univariable and multivariable logistic regression	3
the frequency and types of medication discrepancies (between previous treatment and medication order at admission), and to identify predictors of unintentional medication discrepancies (UMD)	Unintentional medication discrepancies between the BPMH and admission medication were registered.	42%	Age, French-speaking, educational level, admission to ward (no ICU), comorbidities, number of drugs, type of admission, socioprofessional category, living alone	Univariable: Inability to speak French p=0.007, low educational level p=0.004, admission to a hospital ward (no ICU) p=0.019, two or more comorbidities p=0.001, eight or more drugs p=0.004. Multivariable: educational level	Univariable and multivariable logistic regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Coffey 2009	Single center observational prospective cohort study	General pediatric unit	Admission	Admission> 24 hours	272	A research pharmacist obtaining the BPMH NB: medication reconciliation was implemented in the same period
Cornu 2012 'Effect…' Annals of Pharmacotherapy	Single center retrospective cohort study	Geriatric department of university hospital	Admission	≥65 years, ≥ 1 prescription drug at admission, available discharge letter and medication list	199	Comparing medication list after medication reconciliation with admission medication.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
to quantify discrepancies in medication orders at the time of admission. secondary objectives to determine the clinical significance of unintentional discrepancies (ie, errors) and identify associated characteristics.	Unintentional difference between medication from the BPMH with admission orders by discussing with attending physician	22%	Primary admission reason, prevalence of chronic conditions, number of medications, characteristic of home medication (> 4, antiepileptic, cardiac, anticoagulant, and insulin), use of medication reconciliation form	Univariable: ≥4 medications OR 3.22 (95%CI 2.09-4.88), narcotic use OR 1.76 (95%CI 1.05-2.97) anti-epileptic use OR 1.84 (95%CI 1.04-3.28) Multivariable: ≥ 4 medications aOR 12 (95%CI 4-35)	Stepwise logistic regression	5
To determine how often discrepancies In the physician-acquired medication history result in discrepancies during hospitalization and at discharge. Secondary objectives were to determine the influence of clinical pharmacists' Interventions on discrepancies and to investigate possible patient-related determinants for experiencing discrepancies.	Undocumented discrepancies between medication reconciliation by the pharmacist and the admission medication by the physician were classified as unintentional.	81.9%	Age, sex, residential situation (home or nursing home), length of hospital stay, number of drugs in discharge letter	Univariable and multivariable Correctly identified drugs in the clinical pharmacist medication history OR 1.48 (1.25-1.74) aOR 1.47 (1.24-1.74) Information sources used for documenting the medication history OR 1.84 (1.22-2.79) aOR 1.78 (1.13-2.80)	Univariable and multivariable logistic regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Damlien 2015	Single center prospective cohort study	Emergency department	Admission	Patient admitted to the ED	276	Comparing the medication list obtained by the pharmacist/nurse with the medication history obtained by the physician in the ED.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
to develop an innovative prioritizing model for conducting medication reconciliation (MR) at a fast-paced workflow emergency department (ED) and to implement an efficient working model for MR	Clinical relevant medication discrepancy between the list obtained by the pharmacist or study nurse and medication history obtained in the ED	62%	age, sex, cause of admission, who referred the patient to the ED, triage category, living situation, medication registered by physician in ED, number of admission in the last 12 months	Univariable: Age > 60, earlier admission within last 12 months, women and surgical admission, number of medications at admission. ≥ 3 diseases, ≥5 disease. Multivariable model: sex, age, cause of admission and admission within last 12 months.	Chi-square and Mann-Whitney multivariable binary logistic model	6

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
DeCourcey 2017	Single center prospective observational cohort study	Medium and intensive care unit of children's hospital	Admission	<25 years	308	Gold standard preadmission medication list was obtained by a pharmacist and compared to the medication orders. Discrepancies were discussed and scored as intentional or unintentional and as reconciliation potential adverse drug event (PADE) or history PADE

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
to determine the rate, type, timing and predictors of potentially harmful unintentional medication discrepancies in children and young adults with chronic disease	Unintentional medication discrepancies were scored for the potential to cause harm. Potential adverse drug events (PADE) were established.	not given	Gender, age, race, number of preadmission medications, preadmission medication class, admission source, reason for admission, training level admitting clinician, (non) invasive ventilation, markers of medical complexity, number of chronic conditions	Univariable: 18-24 years RR 2.27 (95% CI 1.17-4.42), Non-Hispanic white race (Black RR 0.21 (95%-CI 0.08-0.53), other RR 053 (95%-CI 0.33-0.85), Number of preadmission medications RR 1.09 (95% CI 1.06-1.11), gastronomy tube RR 1.54 (95% CI 1.02-2.33), chronic noninvasive ventilation RR 1.88 (95% CI 1.19-2.95 respiratory medication RR 1.87 (95% CI 1.16--2.99), gastrointestinal medication RR 2.19 (1.23-3.89), neurological medication RR 2.07 (1.29-3.30) Multivariable: Number of preadmission medications RR 1.08 (95% CI 1.05-1.11), chronic respiratory medication RR 1.51 95% CI 1.01–2.28) chronic non-invasive ventilation RR 1.71 (95% CI 1.15-2.53)	Bivariable and multivariable binomial regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Dei Tos, 2020	Single center retrospective observational cohort study	General internal medicine and pulmonology wards of a non-academic hospital	Admission and discharge	≥ 18 years, presented at the emergency department, using ≥1 chronic medication	144	Nurses and physicians are in charge to assess patients' home medication through various sources (patient interview, personal clinical documents, previous hospital letters)
Ebbens, 2018 PDS	Single center observational cross sectional study	Elective surgery patients of general hospital	Admission	≥ 18 years, > 24 hour admission	183	Medication reconciliation consisted of a standardized medication interview with the patient performed by the pharmacy technician.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
Any discrepancy between the information in the medical record and the admission prescription orders with no documented reason for a difference was defined as an unintended medication discrepancy.	The assessment about the patients' homemedications was reported using the information in the medical records by the physician and compare them with the admission prescription orders.	24.3%	Age, sex, home care setting, hospital admission ward, number of comorbidities, main discharge diagnosis, number of medications	6-8 medications OR 3.02 (95% CI 1.10-8.47), >9 medications OR 3.02 (95% CI 2.9-20.96), from nursing home OR 3.29 (95% CI 1.14-9.43) Multivariable > 9 medications aOR 6.06 (95% CI 1.85-21.20)	Univariable and multivariable logistic regression	4
the proportion of POS patients with MEA and to identify risk factors of MEA.	Comparing the result of medication reconciliation at admission to the medication list obtained at the preoperative screening.	32.8%	Age, sex, number of medications at preoperative screening (POS), ASA score, time in days between POS and admission, health literacy, education level, living situation, hypertension, cardiovascular disease, respiratory disease, diabetes mellitus, thyroid disease, cerebral vascular accident, renal disease, epilepsy, thrombosis, conversation score POS	Univariable: Number of medications at POS OR 1.24 (95% CI 1.12-1.37), ASA score OR 2.22 (95% CI 1.38-3.57), cardiovascular disease OR 3.50 (95% CI 1.40-8.75), respiratory disease OR 5.52 (95% CI 2.11-14.44), diabetes mellitus OR 3.22 (95%-CI1.22-8.51) Multivariable: number of medications at POS OR 1.16 (95%CI 1.04-1.30), respiratory disease OR 4.25 (95%CI 1.52-11.83)	Univariable and multivariable logistic regression	6

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Ebbens 2018 Annals	Single center observational quantitative study	Elective surgery patients of university hospital	Admission	≥ 18 years, > 24 hour admission	368	Medication reconciliation consisted of a standardized medication interview with the patient performed by the pharmacy technician.
Falconer 2017	Single center prospective observational study	Cardiology and general medical team	Admission	≥ 18 years	247	Medication reconciliation was performed at admission using at least two sources of information including patient interview.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
To validate this risk prediction model to identify patients at risk for MEAs in a university hospital setting.	Comparing the result of medication reconciliation at admission to the medication list obtained at the preoperative screening.	45.4%	Age, sex, number of medications at POS, time in days between POS and admission, level of education, comorbidities (hypertension, cardiovascular disease, respiratory disease, cerebrovascular accident, kidney disorder, thrombosis/embolism, diabetes mellitus, thyroid disorder)	Univariable and multivariable: Number of medications at POS OR 1.06 (95% CI 1.01-1.12)	Univariable and multivariable logistic regression	6
To validate assessment of risk tool , and to determine which of the selected 25 flags were significantly associated with risk of unintentional medication discrepancies and prescribing errors	Unintentional medication discrepancies were defined as any discrepancy between the patient's original preadmission medication list and the medicine prescribed on the admission chart, where the prescriber was unaware of the discrepancy.	51%	>8 medications at admission, diabetic medications, readmission < 30 days, readmission < 7 days, chronic care program diabetes, poor compliance, age> 75, frequent presenter, cardiovascular medication, English difficulty, outdated pyxis, anticoagulant medications, chronic care program heart failure, opioid mediations, high risk transfer, therapeutic drug monitoring medications, high-ris specialty.	Univariable: > 8 medications OR 3.7 [2.2-6.4], diabetic medications OR 2.4 [1.3-4.6], readmission < 30 days OR 6.8 [3.0-15.2], readmission < 7 days OR 3.5 [1.9-6.4]. Multivariable: > 8 medications aOR 3.7 (95% CI 2.2-6.4) readmission < 30 days aOR 6.8 (95%CI 3.0-15.2)	Binary and multiple logistic regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Gerlier 2019	Single center retrospective observational study	Emergency department	Admission	>24 hour admission weekdays, >72 hour admission weekends	200	Medication reconciliation was performed using multiple sources of information and patient interview
Gleason 2010	Prospective single center cohort study	All inpatients	Admission	All admitted patients	651	Review of electronic medical record combined with an interview with the patient

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
Having at least one unintentional medication discrepancy	Intentional or unintentional medication discrepancies were determined by the pharmacist and responsible physician	56%	Age ≥ 75 years, sex, ≥ 2 comorbidities, residence, able to participate in medication reconciliation, arrive at ED with own transport, busy at the ED, arrive at ED in evening/ night, ≥ 5 medications at admission, prescriptions at evening/night, ≥ 4 intentional discrepancies, prescribing physician, surgical admission	Univariable: ≥ 2 comorbidities OR 2.25 [1.27-3.99], ≥ 5 medications at admission OR 4.41 [2.42-8.02] Multivariable: ≥ 5 medications at admission aOR 1.30 [1.15-1.26]	Univariable and multivariable Logistic regression	6
to determine risk factors and potential harm associated with medication errors at hospital admission.	Discrepancies between result of medication reconciliation and admission medication orders that resulted in medication changes after contact with the prescribing physician were considered medication errors.	35.9%	Age, sex, race, ethnicity, limited English proficiency, number of home mediations, medicare-diagnosis-related group case mix index weight, length of stay, transfer to intensive care, admission to hospitalist or teaching service, multiple pharmacy use, multiple prescribing physicians, recent medication or dosage changes, presentation of mediation list or bottles	Univariable: age, sex, number of prescription medications on admission Multivariable: Age ≥ 65 years aOR 2.17 (95%CI 1.09-4.30), number of preadmission medications aOR 1.21 (95%CI 114-1.29). Protective factor: Presenting medication list upon admission aOR 0.35 (95%CI 0.19-0.63)	Chi-square test, t-test, logistic regression for potential harmful errors	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Gomez 2017	Single center prospective cross-sectional study	internal medicine, geriatrics, and oncology ward of a tertiary university hospital	Admission	Adult patients, Having chronic medication	148	Medication reconciliation was performed including a patient interview
Gonzalez-Garcia 2016	Single center prospective observational study	Surgery department of a regional public hospital	Admission	>18 years, > 48 hours admission	176	Review of electronic clinical records and primary care systems combined with clinical interview.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
The main outcome variable was the number of unjustified discrepancies detected, defined as any discrepancy between the chronic treatment of the patient and his prescription of income that was not justifiable due to your new situation clinic.	Medication reconciliation errors were defined as unjustified discrepancies between home and admission medication after discussing with responsible physician	76.4%	age, number of comorbidities, polypharmacy, and degree of dependency for basic activities of daily living	Univariable: polypharmacy. Multivariate: Polypharmacy aOR 3.4 [1.2-9.0], multiple chronic conditions under 80 years aOR 3.9 [1.07-14.7]	Univariabe and multivariable logistic regression	5
to determine the prevalence of reconciliation errors (REs) at admission to surgery departments, report their potential clinical impact and analyse possible risk factors.	Unjustified discrepancies between chronic medication before hospital admission and medication prescribed in the hospital by discussing with attending physician are considered reconciliation errors.	55.1%	Age, sex, educational level, allergies, number of drugs prior to hospital admission, type of admission	Univariable: Age, number of drugs, admitted for elective surgery Multivariate: number of drugs aOR 1.342 (95%CI 1.210-1.487), elective surgery admission aOR 4.450 (95%CI 2.046-9.688)	Chi-square or Fisher's test and univariable logistic regression. Multivariable logistic regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Guo 2020	Single center prospective observational cohort study.	Cardiology, nephrology, endocrinology, and pneumology department	Admission	≥ 18 years, ≥ 1 regular medication	331	Obtaining the BPMH, verifying and comparing to admission medication orders
Hellstrom 2012	Single center prospective cohort study	Two internal medicine wards of an university hospital	Admission	All admitted patients	670	Medication reconciliation interviews combined with preadmission medication list performed by clinical pharmacist
Huber 2017	Single center prospective implementation study	Vascular and visceral surgery of cantonal hospital	Admission	≥ 16 years, > 48 hour admission	228	Structured interview combined with information from different sources if necessary.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
Prevalence of unintentional medication discrepancies at admission and associated risk factors	Discrepancies were discussed with pharmacists and physicians to indicate whether the discrepancy was unintended.	22.4%	age, sex, type of medical specialty, level of education, living status, the number of drugs taken prior to admission, physician's working experience (intern, resident or attending physician), day of admission (working days, weekends and holidays), type of admission (planned or unplanned), and patient's understanding of preadmission medications.	Univariable: day of admission holiday OR 4.113 (95% CI 1.391-12.157), ≥ 2 chronic diseases at admission OR 2.147 (95% CI 1.557-4.845), > 5 medications on the BPMH OR 3.057 (95% CI 1.767-5.289) Multivariable: ≥ 2 chronic diseases at admission aOR 1.376 (95% CI 0.327-5.791), ≥ 5 medications on the BPMH aOR 3.250 (1.723-6.132)	Univariable and multivariable logistic regression	5
to describe the frequency, type and predictors of errors in medication history, and to evaluate the extent to which standard care corrects these errors. Having at least one unintended medication error	Unintended medication discrepancies that reached the patient were considered medication errors.	63%	Number of drugs at admission, age, sex, type of care service before admission, transfer from other ward	Number of medications at admission aOR 1.10 (95%CI 1.06-1.14), Living at home aOR 1.58 (95%CI 1.02-2.45)	Multivariable binary logistic regression	5
the proportion of patients with at least one medication discrepancy in the medication history at admission before and after intervention (IT guided checklist)	The medication history obtained by the pharmacist was compared to the medication history obtained by the physician. Discrepancies were identified.	69.9% before intervention, 29.6% after intervention	Sex, admission through emergency department, admission for same day surgery, nighttime admission, age, admission indication, home situation (with support or nursing home), hospital stay, IT-guided checklist (intervention)	Age (p=0.015 higher age decreased the odds), IT-guided checklist p < 0.001	Multivariable logistic regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Leguelinel-Blanche, 2014	Single center prospective study with observationaland interventional period	General medicine and infectious and tropical disease ward	Admission	>18 years	394	Observational period retroactive medication reconciliation (MR), interventional period proactive MR using different sources of information and interview the patient creating a BPMH by a pharmacist
Van der Luit 2018	Single center retrospective observational study	Emergency department of general hospital	Admission	≥ 1 medication in use	832	The BPMH is established during medication reconciliation including a semi-structured patient/ caregiver interview

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
The primary outcome was the proportion of patients with one or more UMD identified	Unjustified discrepancies between current admission medication and the BPMH were identified with the physician and considered medication errors	45.8% (observational period), 2.1% (interventional period)	Age, gender, unit, number of medications of the BPMH, number of added medications, number of suspended or stopped medications, number of continued medications	Univariable: Age p<0.005 Number of medications at admission p<0.0001 Multivariable: number of medications on BPMH (3-6) aOR 5.66 (95%CI 1.45-22.02) (≥7 medications) aOR 16.77 (95% CI 3.96-71.04), number of stopped medications aOR 7.75 (95% CI2.21-27.24),, Number of continued medications aOR 3.92 (95% CI 1.86-8.26),	Univariable T-test, Mann-Whitney's test. Multivariable backward logistic regression	5
the proportion of patients experiencing one or more medication discrepancies, as verified by the physician.	Medication discrepancy is defined as an inconsistency between the actual medication in the electronic patient record and the BPMH.	11.7%	Age, sex, type of medical specialty, surgical specialty (vs non-surgical), number of drugs prior to admission.	Univariable: Age OR 1.03 [1.02-1.04], number of pre-admission medications OR 1.13 [1.09-1.17] Multivariable: number of preadmission medications aOR 1.10 [1.06-1.15], age aOR 1.02 [1.01-1.03]	Univariable and multivariable logistic regression	6

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Manias 2009	Single center retrospective chart review design	Unplanned admissions from the emergency department	Admission	≥18 years, emergency department (ED) visit and seen by physician	210	The ED physician would describe all medications at the point of entry at the ED by patient interview. At discharge from the ED description of the ordered medication was documented by the admitting physician
Marinovic 2016	Single center, Prospective observational study	Clinical department of internal medicine of a teaching hospital	Admission	≥18 years, ≥ 1 prescription medication	411	Medication reconciliation was performed by a clinical pharmacist within 24 hours of admission. A patient interview was undertaken using a standardized BPMH form.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
patients having had at least one medication discrepancy without appropriate clinical explanation	Medication discrepancies were differences between the drugs on the medication chart by the attending physician and the admission medication from the ED. Unjustified medication discrepancies were analyzed.	34.8%	Age, chief complaint, need for interpreter, benefit card holder, sex, hearing deficit, visual deficit, < 5 drugs at the ED, known drug allergy, length of time in the ED, physician wait time in ED, triage code, mode of arrival, inpatient admission, discharge destination, physician level, absence of pharmacist in ED, seen by physician within 1 h of shift change, arrival time at the ED, discharge time from the ED, time first seen by physician.	Univariable: age, need for interpreter, benefit card holder, visual deficit, ≥ 5 drugs in the ED, known drug allergy, inpatient admission, discharge destination surgical unit, seen by physician within 1h of shift change. Multivariable: Benefit card holder aOR 3.73 (95% CI 1.72-8.07), ≥ 5 drugs ordered at discharge from ED aOR 12.22 (95% CI 5.52-27.08), seen by physician within 1 h of shift change aOR 3.70 (95% CI 1.67-8.18), Physician wait time (minutes) aOR 1.01 (95% CI 1.00-1.01)	Univariable: Chi-square test and binary logistic regression Multivariable: Binary logistic forward stepwise regression	6
the frequency, type, and potential severity of unintentional medication discrepancy	BPMH was compared to admission orders and discrepancies were communicated with physicians in order to clarify if changes were intentional or unintentional. Unintentional medication discrepancies were considered medication errors	35%	Age, sex, educational level, employment status, residence, type of hospital admission, comorbidities, readmission medication, history of adverse drug events, recent hospitalization, length of hospital stay, level of patients' understanding of preadmission medication.	Number of medications aOR 1.19 (95% CI 1.10-1.29). Low level of patients understanding aOR 1.79 (95% CI 1.01-3.16)	Multivariable logistic regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Mazhar, 2017	Single center cross-sectional study	Cardiology, endocrinology and surgical department of tertiary teaching hospital	Admission	>24 hour admission, existing drug therapy on admission	328	Comprehensive structured interview with patient and/or caregiver to obtain medication use history
Rentero 2014	Cross-sectional study	Cardiology, neurology, traumatology and urology department	Admission	≥ 18 years, >24 hour admission	221	The pharmacist carried out the home pharmacotherapy history through structured interview with the patient / caregiver

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
The primary endpoint of the study was the presence of reconciliation error.	A medication discrepancy was defined as any difference between medications taken by a patient prior to admission and medications ordered upon admission. Discrepancies were than categorized in intentional and unintentional discrepancies.	54%	Gender, age (> 65 years), type of admission (emergency/scheduled), day of admission (weekdays vs weekend), professional category (pharmacist, resident, nurse), medication list or medication bag available on admission, polypharmacy, comorbidities, hypoglycemic drugs, warfarin,	Univariable: Male OR 0.79 (95%-CI 0.3-0.9), ≥ 65 years OR 3.62 (95%CI 2.1-6.4), polypharmacy OR 8.23 (95%CI 3.8-17.8), comorbidities OR 3.84 (95%CI 2.1-6.9), hypoglycemic drugs OR 2.71 (95%CI 1.2-5.8), warfarin OR 3.06 (95% CI 0,7-12.2) Multivariate: ≥ 65 years aOR 2.7 (95%CI 1.5-5.1), Polypharmacy aOR 5.3 (95%CI 2.4-11.6), hypoglycemic drugs aOR 2.6 (95% CI 1.1-6.2), warfarin aOR 3.4 (95%CI 2.9-7.1)	T-test, chi-square test. Multivariable logistic regression analysis using a stepwise forward 'LR" procedure	5
to determine the main causes of errors of medication reconciliation at hospital admission in medical and surgical department and establish factors associated with medication reconciliation errors.	Reconciliation errors were defined as unjustified discrepancies between the home pharmacotherapy and the prescription at admission	58.4%	sex, age, comorbidities, type of income, income service, professional category of the person performing the anamnesis, active medication, therapeutic group, polypharmacy, sources of information, duration of the interview.	Multivariate: age > 65 years aOR: 2.7 [95% CI: 1.5 - 5.1], polypharmacy aOR: 5.6 [95% CI: 2.5 - 12.6] and taking antidiabetics Orally aOR: 2.6 [95% CI: 1.1– 6.2].	Multivariate logistic regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Rodriquez Vargas 2016	Single center prospective observational study	Internal medicine, infectious disease, orthopedic surgery and general surgery units of tertiary hospital	Admission	>65 years, ≥ 5 medications prior to admission, >48 hour admission	206	BPMH was obtained within 24 hours of admission by a pharmacist, using hospital records, medication list from emergency department, and standardized patient interview
Salameh 2018	Single center prospective observational study	Internal medicine department of tertiary university teaching hospital	Admission	≥ 18 years, ≥ 4 regular prescription medications, >48 hour admission	200	A comprehensive interview was conducted to obtain or verify patient's pre-admission list.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
prevalence of medication reconciliation errors at admission.	BPMH was compared to active inpatient medications. Discrepancies were discussed with the physician. When the physician decided to change the prescription thiswasconsidered a medication reconciliation error.	49.5%	Sex, age, patients' home, number of comorbidities, number of previous surgeries, day of admission, hospitalization unit, type of admission, admitting physician experience, number of preadmission medications, number of medications prescribed at hospital.	Univariable: number of comorbidities p =0.008, number of previous surgeries p=0.025, number of pre-admission medications p<0.01 Multivariate: Admitting physician experience aOR 1.85 (95% CI 1.01-3.40), number of previous surgeries aOR 1.23 (95% CI 1.00-1.52), use of CPOE system aOR 0.43 (95% CI 0.21-0.89), number of preadmission medications aOR 1.20 (95% CI 1.07-1.34)	univariable logistic regression and multivariable forward stepwise logistic regression	5
to identify the prevalence and types of medication discrepancies at the time of hospital admission to a tertiary care teaching hospital in Jordan and to identify risk factors affecting the occurrence of these discrepancies.	All undocumented were discussed with the responsible residence, when no justified cause was found, the discrepancies was reported as unintentional.	47%	Age, gender, educational level, monthly income, CCI, number of pre-admission medications, number of admission medications, number of comorbidities, hospital length of stay, residents' gender	Univariable: age, gender, educational level, residents gender Multivariable: Age p=0.013, treated by female resident p=0.045	Simple and multiple linear regression	4

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Salanitro 2012	Cross-sectional analysis of intervention group of two center randomized controlled trial	Cardiac patients in two academic hospitals	Admission and Discharge	≥18 years, admitted with acute coronary syndrome or acute decompensated heart failure	423	Study pharmacists obtain a pre-admission medication list (PAML) and compare this to the physician's PAML, the admission orders and discharge orders
Silvestre 2017	Single center prospective case-control study	Surgical, medical and pediatric ward of a teaching hospital	Admission	>24 hour admission	358	A clinical pharmacist analysed the medical records and assessed the presence of unjustified medication discrepancies.

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
To identify patient- and medication-related factors that contribute to pre-admission medication list (PAML) errors and admission order errors, and to test whether such errors persist in the discharge medication list.	All unintentional medication discrepancies were considered to be errors. Three outcomes were assessed, 1 PAML errors, 2 admission errors, 3 discharge errors.	19% admission error	Age (<55, 55-65, 65+), living alone vs not, insurance type, health literacy, cognition level, medication understanding, medication adherence, number of preadmission prescription medication, medication list available in electronic medical record, medication changes.	Admission, adjusted: age IRR 1.84 (95% CI 1.26-2.70), number of pre-admission medications IRR1.07 (95% CI 1.01-1.14).	Negative binomial logistic regression for all three outcomes	5
we examined potential risk factors for unintended medication discrepancies (UMD) identified at admission	Unjustified medication discrepancies are defined as erroneous and unjustified medication changes between the medication use history and the admission medication orders.	N/a	Sex, age, marital status, literacy and salary income, number of prescribed drugs before admission, clinical ward, interhospital transfers.	Interhospital transfers adults aOR 2.80 (95%-CI 1.09-7.14), children aOR 3.02 (95%CI 1.23-7.28).	Logistic regression	4

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Stuijt 2017	Multi center retrospective cohort study	Six hospitals with at least five years of medication reconciliation experience	Admission and discharge	All patients using chronic medication	765	Pharmacy technicians perform medication reconciliation and discuss any discrepancies with the physician to resolve these.
Unroe 2010	Single center retrospective chart review	General medicine, cardiology, or general surgery services of tertiary academic teaching hospital	Admission	Adult patients	178	Within 48 hours of admission a clinical pharmacist reviewed patient histories obtained by the provider ant nurse and compared them with medication prescribed on admission. When discrepancies were found the pharmacist investigated further by interviewing the patient and/ or physician, or pharmacy

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
presence or absence and number of interventions on admission and discharge	Interventions are defined as corrections to resolve unintended medication discrepancies. If a physician did not accept a suggested intervention this was regarded as an intentional medication change.	74.5%	Number and type of medication for chronic use, use of high risk drugs, having had an admission interview, admission type (acute vs elective), age, gender, social circumstances, social class (on postal code).	Univariable: Age OR 1.02 (95% CI 1.00-1.03), Acute admission OR 2.05 (95% CI 1.31-3.20), number of admission medications OR 1.11 (95% CI 1.05-1.45), number of high-risk medications OR 1.23 (95% CI 1.05-2.45) Multivariable: Acute admission aOR 2.11 (95% CI 1.33-3.35), number of admission medications aOR 1.10 (95% CI 1.05-1.16), age aOR 1.01 (95% CI 1.00-1.03)	Chi-square test, generalized linear mixed effects models and multi-level Poisson regression	6
to describe the incidence, drug classes, and probable importance of hospital admission medication discrepancies and discharge regimen differences, and to determine whether factors such as age and specific hospital services were associated with greater frequency of medication discrepancies and differences.	Medication discrepancies are defined as any changes in a patient's previous medications that were identified by an inpatient pharmacist as unintended and potentially clinically relevant at the time of the patient's admission.	23%	Univariable: Age, sex, race, number of comorbidities, admitting services (general medicine, general surgery vs cardiology), number of medications on admission, any high-risk medications on admission Multivariable: age, admitting services, any high-risk medications on admission.	Univariable: Presence of high-risk medication OR 63.14 (95%CI 7.93-502.45), admitting service (general surgery vs cardiology) OR 3.21 (95%CI 1.29-7.98). Multivariable: age (per 5 year) aOR 1.16 (95%CI 1.01-1.33), presence of high-risk medications aOR 76.68 (95%-CI 9.13-643.76), general surgery service aOR 3.31 (95%CI 1.40-7.87).	Logistic regression	5

Table 1. (continued)

Author year	Study Design	Setting	Admission and/or discharge	Most important inclusion criteria	Sample size	Medication reconciliation method
Zoni 2012	Single center pre-post intervention study	Department of internal medicine of third-level public hospital	Admission	≥ 3 medications prior to admission, >24 hour admission	162 (80 pre intervention, 82 post intervention)	BPMH was obtained for all patients. Pre-intervention physicians were not trained to consult the BPMH while prescribing admission prescriptions. Post intervention physicians were trained to do so

Abbreviations: OR: Odds Ratio; aOR: adjusted Odds Ratio; 95%-CI: 95% Confidence Interval, ME: medication error, RE: reconciliation error, BPMH: best
classification system, UMD: unintentional medication discrepancy, NB: nota bene, ie: in other words, ED: emergency department, MR: medication reconcili
of Anesthesiologists physical status classification. PAML: preadmission medication list, IRR: incidence rate ratio, n/a: not applicable

Table 2. Characeteristics of reviewed studies at discharge

Author year	Study Design	Setting	Admission or discharge	Most important Inclusion criteria	Sample size	Medication reconciliation Method
Akram 2015	Single center Retrospective clinical record review	Internal medicine wards of University hospital	Discharge	≥ 65 years Traceable prescription in CPRS database and one of 21 chronic diseases	150	Preadmission and discharge medication lists were compared for any discrepancy
Breuker 2016	Single center prospective observational study	Endocrinology, Diabetology and Nutrition department	Admission and Discharge	> 18 years >24 hour admission	904	Medication reconciliation using patient records and structured patient interview

Endpoint/ outcome	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS
The main outcome measures were the cumulative incidence of unintended discrepancy defined as the total number of unintended discrepancies over the total of drugs prescribed expressed as a percentage and the proportion of patients with at least one unintended discrepancy.	Admission prescriptions were compared to the BPMH. When unintended medication discrepancies were found the prescriber was contacted to solve this.	Pre-intervention: 23.7% Post-intervention: 14.6%	Age, gender, date of admission, comorbidities (hypertension, asthma, diabetes mellitus type I, diabetes mellitus type II, heart failure, dyslipideamia, COPD, thyroid disorders, depression, peptic ulcers, allergies, renal or liver failure).	Univariable: asthmatic patients p = 0.01, diabetes mellitus type 1 p=0.03 Multivariable: having asthma OR 6.37 (95% CI 1.6-25.5)	Chi-square, t-test. Univariable and stepwise backward multivariable logistic regression	4

t possible medication history, NOS: Newcastle-Ottawa quality assessment scale, WHO: world health organization, ATC: anatomical therapeutic chemical ation, PADE: potential adverse drug events, RR: rate ratio, POS: preoperative screening, MEA: medication error at admission, ASA score: American Society

Endpoint/ outcome; objective/ aim	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS criteria
Having at least one unintentional discrepancy	Unintentional discrepancy: one that lacked any documentation of medication change in either the clinical record or the discharge summary	23.3%	Age, gender, number of comorbidities, functional status, number of medications, number of discrepancies on discharge (including intentional).	Univariable and multivariable: Number of discrepancies per patient on discharge (including the intentional) aOR 1.29 (95%CI 1.06-1.56).	Univariable and multivariable logistic regression	4
Number of patients with medication (transfer) errors.	Medication errors are defined as unintended discrepancies corrected by the physician.	1.6%	Model 1: Having diabetes Model 2: having diabetes, admission period, number of prescription lines Model 3: model 2 + age and sex.	Discharge: Univariable diabetes OR 1.96 (1.06-3.63). Multivariable no significance.	Univariable and multivariable logistic regression	3

Table 2. (continued)

Author year	Study Design	Setting	Admission or discharge	Most important Inclusion criteria	Sample size	Medication reconciliation Method
Breuker 2017 DM	Single center prospective observational study	Diabetology department of university hospital	Admission and Discharge	> 18 years >24 hour admission	671	Medication reconciliation using patient records and structured patient interview
Breuker 2017 JPS	Single center prospective observational study	Endocrinology, Diabetology and Nutrition department	Admission and Discharge	>18 years	904	Medication reconciliation using patient records and structured patient interview
Caleres 2019	Multicenter descriptive study	150 different department from ten hospitals	Discharge	≥ 75 years, ≥ 5 drugs	933	Pharmacists performed a comprehensive retrospective medication history. All information was combined into a supposedly correct discharge medication list

Endpoint/ outcome; objective/ aim	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS criteria
Patients with at least one medication error.	Medication errors are defined as unintended discrepancies corrected by the physician.	29.4%	Age, number of treatment lines in prescription, type of diabetes.	No significant risk factor found	Multivariate Logistic regression	3
Patients with at least one medication error.	Medication errors are defined as unintended discrepancies corrected by the physician.	29.4% 179/904 (admission), 87/904? (discharge)	Age, sex, BMI, admission reason, associated chronic diseases, number of chronic diseases, type of admission, time of admission, length of stay, living area, number of medications	Univariable: Age OR 1.02 (95% CI 1.01-1.03), number of chronic diseases p<0.001, admitted for diabetic foot p=0.02, emergency admission p=0.01, number of medications p<0.001. Multivariate discharge adjusted for number of treatments: no significant factors.	Univariate and multivariate Logistic regression	3
medication discrepancy rate and types for discharge summaries for elderly patients with many drugs,	The compiled discharge medication list was compared to the medication information in the discharge summary to identify unintentional medication discrepancies.	38%	Multi-dose drug dispensing, discharge to nursing home, pharmacist medication reconciliation, sex, discharge day/ weekend, age, number of drugs, number of drug changes, department type (reference geriatrics), discharging physician (resident/specialist), team-based medication review	Univariate: multi-dose drug dispensing OR 4.0 (95%CI 2.95-5.42), discharge to nursing home OR 1.89 (95% CI 1.38-2.59), age OR 1.03 (1.01-1.06), number of drugs OR 1.10 (95% CI 1.07-1.14), department of surgery OR 2.54 (95% CI 1.37-4.68), department of orthopaedics OR 2.20 (95% CI 1.15-4.23), department of infectious disease OR 2.86 (95% CI 1.29-6.38). Multivariate: Multi-dose drug dispensing aOR 3.42 (95% CI 2.48-4.74), number of drugs aOR 1.09 (95% CI 1.05-1.13), department of surgery aOR 2.96 (95% CI 1.55-5.66), department of oncology aOR 3.86 (95% CI 1.24-12.1), drug changes aOR 0.93 (95% CI 0.88-0.99)	Univariate and multivariate logistic regression	5

Table 2. (continued)

Author year	Study Design	Setting	Admission or discharge	Most important Inclusion criteria	Sample size	Medication reconciliation Method
Cornu 2012 'Discrepancies …'	Single center retrospective cohort study	Geriatric department of university hospital	Discharge	≥65 years, medication reconciliation performed at admission, available discharge letter and medication list	189	Comparing the discharge medication list with medication information in the discharge letter
Dei Tos, 2020	Single center retrospective observational cohort study	General internal medicine and pulmonology wards of a non-academic hospital	Admission and discharge	≥ 18 years, presented at the emergency department, using ≥1 chronic medication	144	Nurses and physicians are in charge to assess patients' home medication through various sources (patient interview, personal clinical documents, previous hospital letters)

Endpoint/ outcome; objective/ aim	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS criteria
To determine the incidence and type of discrepancies between the discharge letter for the primary care physician and the patient discharge medication list as well as identify possible patient-related determinants for experiencing discrepancies.	Any undocumented discrepancies between the discharge medication list and medication information in the discharge letterisconsidered unintentional	47.6%	Age, sex, residential situation (home or nursing home), length of hospital stay, number of drugs in discharge letter	Univariate Number of drugs at discharge OR 1.18 (95% CI 1.07-1.32) Multivariate Number of drugs at discharge aOR 1.20 (95%CI 1.08-1.34)	Univariable and multivariable logistic regression	5
Any discrepancy between the information in the medical record and the discharge prescription orders with no documented reason for a difference was defined as an unintended medication discrepancy.	The assessment about the patients' homemedications was reported using the information in the medical records by the physician and compare them with the discharge prescription orders.	27.1%	Age, sex, home care setting, hospital admission ward, number of comorbidities, main discharge diagnosis, length of stay, number of medications	Univariable: >9 medications OR 5.58 (95% CI 2.27-14.28), discharge to nursing home OR 6.6 (95% CI 2.76-16.51), length of stay 8-10 days OR 4.10 (95% CI 1.254-15.01, length of stay 11-15 days OR 5.47 (95% CI 1.88-18-47), length of stay ≥16 days OR 3.35 (95% CI 1.03-12.09) Multivariable > 9 medications aOR 7.55 (95% CI 2.02-32.27), discharge to nursing home aOR 5.53 (95% CI 1.27-30.39), length of stay 8-10 days aOR 5.78 (95% CI 1.27-30.39), length of stay 11-15 days aOR 5.34 (95% CI 1.4-23.85), length of stay ≥16 days aOR 5.97 (95% CI 1.29-31.56)	Univariable and multivariable logistic regression	4

Table 2. (continued)

Author year	Study Design	Setting	Admission or discharge	Most important Inclusion criteria	Sample size	Medication reconciliation Method
Garcia-Molina 2015	Single center cross-sectional study	Cardio-pulmonology unit of a general hospital	Discharge	≥ 18 years, taking medication, >48 hour admission,	216	Home medication was established by a structured interview combined with information from multiple sources.
Geurts 2013	Retrospective single site study in a community pharmacy	Community pharmacy	Discharge	Independently living patients discharged from a hospital	100 discharges in 83 patients	Review of discharge letter, discharge prescriptions and medicine card. Discrepancies were discussed with discharging physician and the reconciled discharge medication discussed with the patient

Endpoint/ outcome; objective/ aim	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS criteria
Any difference between preadmission medication and the postdischarge treatment was considered a discrepancy. Any discrepancy that could not be clinically justified was considered a reconciliation error (RE).	Unjustified medication discrepancy between preadmission and postdischarge medication after clarification by responsible physician. Including: In cases where the physician had used the expression "continue home medication", the medicines that should have appeared on the discharge report were considered as errors of omission	88.9%	Polypharmacy at admission, number of drugs at admission, pluripathology, age, sex, patient provenance, length of stay, day of discharge, bed occupancy, number of admissions per day, number of discharges per day, stay in another unit, time until interview, source of information concerning medication provided by the patient, medication adherence (Morisky-Green test)	Univariate: Polypharmacy at admission, 5-8 drugs at admission, poluripathology, age of 66-80 years, emergency admission, specialist physician responsible for discharge, more than 24 h until interview, prescription bottles ore medical reports provided by the patient. Multivariate: Polypharmacy at admission aOR 27.02 (95%CI 8.78-83.42), discharge report signed by a specialist physician aOR 5.22 (95%CI 1.40-19.42) and emergency admission aOR 3.15 (95% CI1.07-9.29)	Simple and multivariate logistic regression	5
Number, type and origin of discrepancies for all independently living patients discharged from the hospital	All discrepancies within discharge documents, between discharge documents and the information in the computer system were included.	73%	Different hospital settings (university and general), sex, length of admission, age, medicines before admission, medicines at discharge	Medication at discharge OR 1.098 (95% CI 1.009-1.195)	Poisson regression analysis	6

Table 2. (continued)

Author year	Study Design	Setting	Admission or discharge	Most important Inclusion criteria	Sample size	Medication reconciliation Method
Grimes 2011	Two center cross-sectional observational healthcare record review survey	Inpatients from different services to reflect a range of general medical and surgical care in two academic hospitals	Discharge	≥ 16 years	1245 (episodes of care)	Medication reconciliation at admission was performed by a clinical pharmacist
Herrero-Herrero 2011	Single center retrospective cohort study	Internal medicine service of tertiary university hospital	Discharge	≥ 65 years discharge report had to be complete	954 discharge reports in 790 patients	Information from available records and structured interview on admission

Endpoint/ outcome; objective/ aim	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS criteria
Primary outcome was medication non-reconciliation, defined as a prescription writing error on the discharge communication or a failure to document or communicate medication changes on the discharge communication (prescription or summary)	Medication non reconciliation defined as a prescription writing error on the discharge communication or a failure to document or communicate medication changes on the discharge communication	50.1%	GMS card status, hospital, discharge process, medical/surgical care, age, length of stay, chronic or acute illness, number of medications	Chronic illness aOR 2.08 (95%CI 1.33-3.24), Handwritten discharge process aOR 1.60 (95%CI 1.11-2.99), Number of medications aOR 1.26 (95% CI 1.21-1.31)	Binomial logistic regression	6
the number and type of unjustified discrepancies between treatment at admission and at the time of hospital discharge (errors in medication reconciliation)	Discrepancies were categorized as justified or unjustified using additional information in the discharge report	5.4%	Age, sex, cognitive impairment, nursing home, length of stay, discharge in weekend days, number of diagnosis, number of permanent medicines at admission, number of permanent medicines at discharge	Number of permanent medications at admission univariate p= 0.005 multivariate aOR 1.123 (95% CI 1.034-1.219)	Chi-square, Fisher's exact test, unpaired T-test, Multivariate Logistic regression	5

Table 2. (continued)

Author year	Study Design	Setting	Admission or discharge	Most important Inclusion criteria	Sample size	Medication reconciliation Method
Osorio 2014	Single center prospective observational study	All inpatient medical floors an outpatient office practice	Discharge	≥18 years, discharged to home, outpatient visit < 30 days of discharge	100	Telephone medication interview within 10 days after outpatient visit and outpatient electronic health record review of outpatient clinic compared to hospital discharge medication list
Salanitro 2012	Cross-sectional analysis of intervention group of two center randomized controlled trial	Cardiac patients in two academic hospitals	Admission and Discharge	≥18 years, admitted with acute coronary syndrome or acute decompensated heart failure	423	Study pharmacists obtain a pre-admission medication list (PAML) and compare this to the physician's PAML, the admission orders and discharge orders

Endpoint/ outcome; objective/ aim	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS criteria
to describe the epidemiology of unexplained medication discrepancies and identify patient risk factors for these discrepancies.	Unexplained medication discrepancies defined as changes between the hospital discharge medication list and the list documented by the outpatient provider at the time of first post-discharge ambulatory visit. Information from the health record and telephone patient interview was used.	82%	Age, sex, patient reported prescription medications, educational level, income, English proficiency, outpatient visits in past year, number of providers seen in past year, number of comorbidities, physician experience at follow-up visit, provider's subspecialty at the follow-up visit.	Univariate ($p< 0.05$): patient reported prescription medications 11-26, outpatient visits in past year. Less than high school education, private insurance, high income, > 5 outpatient visits past year. Multivariate corrected for age, gender, income.11-26 medications aOR 2.36 (95% CI 1.16-4.82) > 5 outpatient visits past year aOR 2.39 (95% CI 1.04-5.48), having less than high school education aOR 1.85 (95% CI 1.16-2.95). Medicaid insurance aOR 0.39 (95% CI 0.21-0.75) outpatient visit by third-year resident aOR 0.46 (95% CI 0.23-0.91)	Univariate regression and negative binomial regression	5
To identify patient- and medication-related factors that contribute to pre-admission medication list (PAML) errors and admission order errors, and to test whether such errors persist in the discharge medication list.	All unintentional medication discrepancies were considered to be errors. Three outcomes were assessed, 1 PAML errors, 2 admission errors, 3 discharge errors.	40%	Age (<55, 55-65, 65+), living alone vs not, insurance type, health literacy, cognition level, medication understanding, medication adherence, number of preadmission prescription medication, medication list available in electronic medical record (EMR) , medication changes.	Discharge, adjusted: Living alone vs not IRR 0.67 (95% CI0.47-0.96), number of medication changes during hospitalization IRR 1.08 (95% CI1.03-1.13)	Negative binomial logistic regression for all three outcomes	5

Table 2. (continued)

Author year	Study Design	Setting	Admission or discharge	Most important Inclusion criteria	Sample size	Medication reconciliation Method
Stuijt 2017	Multi center retrospective cohort study	Six hospitals with at least five years of medication reconciliation experience	Admission and discharge	All patients using chronic medication	765	Pharmacy technicians perform medication reconciliation and discuss any discrepancies with the physician to resolve these.
Ziaeian 2012	Single center prospective observational cohort study	Medicine service of urban hospital	Discharge	≥65 years, admitted for acute coronary syndrome, heart failure or pneumonia	377	Discharge instructions are generated electronically with no active reconciliation process. Patients were interviewed within 1 week of discharge

Abbreviations: OR: Odds Ratio; aOR: adjusted Odds Ratio; 95%-CI: 95% Confidence Interval, ME: medication error, RE: reconciliation error, NOS: Newcastle-Ottawa quality assessment scale, ED: emergency department, MR: medication reconciliation, RR: rate ratio, PAML: preadmission

Endpoint/ outcome; objective/ aim	Definition of medication error (ME)/ discrepancy	Patients with ME (%)	Risk factors analysed	Risk factors identified	Statistical analysis	Quality NOS criteria
presence or absence and number of interventions on admission and discharge	Interventions are defined as corrections to resolve unintended medication discrepancies. If a physician did not accept a suggested intervention this was regarded as an intentional medication change.	35.7%	Number and type of medication for chronic use, use of high risk drugs, having had an admission interview, admission type (acute vs elective), age, gender, social circumstances, social class (on postal code). For discharge also length of stay	Number of medications aOR 1.11 (95% CI 1.05-1.16)	Chi-square test, generalized linear mixed effects models and multi-level Poisson regression	6
Medication reconciliation accuracy was determined by comparing the discharge medication list to the admission medication list.	Medication reconciliation accuracy was determined by comparing discharge medication list to admission medication lists. After chart review medication modifications that did not appear to be intended were classified as suspected provider errors.	27.3%	Non relevant medication (not relevant to admission indication), medical team, ACS, heart failure, pneumonia, redosed medication, total number of medications, length of stay, age, sex, race, education level, comorbidity score	Non-relevant medication aOR 4.56 (95%CI 2.65-7.85), Pneumonia aOR 0.33 (95%CI 0.12-0.93), Length of stay aOR 0.91 (95%CI 0.84-0.99)	Multivariable logistic regression	5

medication list, IRR: incidence rate ratio, n/a: not applicable, EMR: electronic medical record, BMI: body mass index, GMS: general medical services, ACS: acute coronary syndrome.

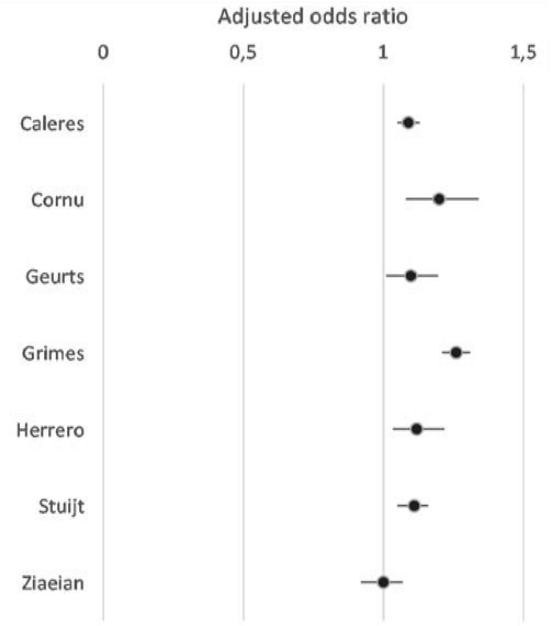

Figure 3. Adjusted odds ratios of number of medications at discharge with 95% confidence intervals from the different studies.

Top 5 independent risk factors of medication errors at discharge

The top 5 of independent risk factors of discharge medication errors is discussed below. In Appendix 3 all independent risk factors of medication errors at discharge are presented.

1. Number of medications

Eleven studies on independent risk factors looked at number of medications. Nine[47-53, 58, 59] out of eleven (77%) found this to be a significant risk factor. Three studies[49, 53, 58] analyzed the number of medications in categories and found a range of 5 or more medications up to 11-26 medications in use to increase the risk of medication errors. The other six studies[47, 48, 50-52, 59] analysed the number of medications as a continuous variable, and reported adjusted odds ratios between 1.09 and 1.26 for each additional medication. Of the two studies that did not find number of medications to be a significant risk factor, one[54] analysed the number of medication as a continuous variable, the other reported number of medications not be significant with no incidence rate ratio reported[7]. The odds ratios of the eight studies that analysed number of medications as continuous variable in multivariable logistic regression are summarized in Figure 3.

2. Physician level

All two studies that investigated physician level as a risk factor found this to be a significant independent risk factor. One study found a 2 to 3 year resident who discharged

the patient to have less risk of medication errors compared to 1 year residents, with an aOR of 0.46.[53] The third study found that discharge by a medical specialist increased the odds of a medication error at discharge compared to residents with an aOR of 5.22.[49]

The next 2 independent risk factors were both found in two studies out of three they were studied in. The order in which they are presented is random.

3. Medication changes during hospitalisation

Two[7, 47] out of three studies found the number of medication changes to be a significant independent risk factor. The results are conflicting in that these studies analysed the number of medication changes as a continuous variable and one found an IRR of 1.08[7] whereas the other found an aOR of 0.93 indicating less risk of medication errors with every additional medication change.[47]

4. Hospital ward of admission

Two studies found the ward of admission to be a significant independent risk. Emergency admissions with an aOR of 3.15[49] and surgery and oncology ward admissions with an aOR of 2.96 and 3.86 respectively[47]. The third study did not show a significant association of pulmonology ward admission versus general internal medicine admission.[58]

5. Residential situation

Two out of four studies found residential situation to be a significant independent risk factor. Living alone was found to be protective versus not living alone with an IRR of 0.67[7]. Discharge to a nursing home was found to be a risk factor of medication errors at discharge with an aOR of 5.53[58]. However, two other studies did not show a significant association of nursing home vs living at home.[48, 52]

DISCUSSION

The most prevalent independent risk factor identified both at admission and discharge is number of medications. This is in accordance with the findings of Hias et al.[16]. At admission, age is the second most common independent risk factor in accordance with earlier findings[16]. However, at discharge, age is tested in eleven studies and none of these found age to be an independent risk factor of medication errors. After the number of medications and age at admission there is no other risk factor that is found in more than a quarter of included studies. At discharge, this is even more profound: only the number of medications is identified as an independent risk factor in more than a quarter of studies. This illustrates the lack of unambiguous risk factors in this field.

The included studies differ in study design, definition of medication errors and the definition of medication. The percentage of patients with medication errors varied widely, which may be caused by differences in study design. Almost all studies took

place in a particular department of the hospital, therefore the patient population differed with respect to comorbidities and type of medication. In addition, a substantial part of the studies included older patient (≥ 65 years) and/or patients that use at least one or at least five medications. This could explain why age is not found in every study as a risk factor.

In order to limit the variation in the definition of medication transfer errors we used a strict definition as an inclusion criterion. With this strict definition we excluded studies that other reviews like Hias et al. did include. Nevertheless, we still found a broad range of percentages of patients with at least one medication error. Probably the definition of unintentional medication errors still differs between studies.[16]

Whether the definition of medication included over the counter medication differed between studies. Some studies specifically included over the counter medication in the medication overview, while others excluded the over the counter medication, and most studies do not explicitly state including or excluding over the counter medication. This may have resulted in different average medication use between studies. Also, the use of over-the-counter medication could lead to more medication transfer errors because in medication reconciliation these medications are often forgotten. Studies that include the use of over-the-counter medication may therefore find number of medications more often as a risk factor of medication errors.

Some limitations need to be addressed. We included all studies on independent risk factors of medication transfer errors at hospital admission or discharge regardless of which risk factors they studied. If only studies were included that investigated the same risk factors we could have drawn more robust conclusions. However, due to the heterogenous study design, only a few studies would have remained in the review when applying more strict inclusion criteria. In addition, the risk of publication bias could have influenced the results of this systematic review. When studies without significant results are less often published the association of the identified risk factors with medication errors may be smaller or non-existent.

A strength of this review is that the broad inclusion of all study designs leads to a very complete overview of the current literature on risk factors of medication transfer errors at hospital admission and discharge. However, the lack of unambiguous risk factors found in studies suggests that there are risk factors not yet identified that could predict the risk of medication errors better. This may be caused by the fact that the choice of potential risk factors to be analyzed is usually based on previous research. Perhaps analyses of big data would be helpful to identify risk factors that have not been explored before.

In order to be able to use the risk factors identified in this systematic review to predict which patients are at increased risk, further research is needed. Future studies should focus on creating risk prediction models that can be integrated in regular care to predict patients at high risk of medication errors. This would make it possible to focus the costly medication reconciliation process on high risk patients.

CONCLUSION

The number of medications used by a patient is the most frequently identified independent risk factor of medication transfer errors at hospital admission and discharge.

REFERENCES

1. Tam, V.C., et al., *Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review.* CMAJ, 2005. **173**(5): p. 510-515.
2. Michaelsen, M.H., et al., *Medication Reconciliation at Discharge from Hospital: A Systematic Review of the Quantitative Literature.* Pharmacy, 2015. **3**(2): p. 53-71.
3. Kwan, J.L., et al., *Medication reconciliation during transitions of care as a patient safety strategy: a systematic review.* Ann Intern. Med, 2013. **158**(5 Pt 2): p. 397-403.
4. Gleason, K.M., et al., *Results of the Medications at Transitions and Clinical Handoffs (MATCH) study: an analysis of medication reconciliation errors and risk factors at hospital admission.* J Gen Intern. Med, 2010. **25**(5): p. 441-447.
5. Pippins, J.R., et al., *Classifying and predicting errors of inpatient medication reconciliation.* J Gen Intern. Med, 2008. **23**(9): p. 1414-1422.
6. Unroe, K.T., et al., *Inpatient medication reconciliation at admission and discharge: A retrospective cohort study of age and other risk factors for medication discrepancies.* Am J Geriatr Pharmacother, 2010. **8**(2): p. 115-126.
7. Salanitro, A.H., et al., *Effect of Patient- and Medication-Related Factors on Inpatient Medication Reconciliation Errors.* Journal of General Internal Medicine, 2012. **27**(8): p. 924-932.
8. Cheema, E., et al., *The impact of pharmacists-led medicines reconciliation on healthcare outcomes in secondary care: A systematic review and meta-analysis of randomized controlled trials.* PLoS One, 2018. **13**(3): p. e0193510.
9. McNab, D., et al., *Systematic review and meta-analysis of the effectiveness of pharmacist-led medication reconciliation in the community after hospital discharge.* BMJ Qual Saf, 2018. **27**(4): p. 308-320.
10. Mekonnen, A.B., A.J. McLachlan, and J.A. Brien, *Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis.* J Clin Pharm Ther, 2016. **41**(2): p. 128-144.
11. Mueller, S.K., et al., *Hospital-based medication reconciliation practices: a systematic review.* Arch Intern. Med, 2012. **172**(14): p. 1057-1069.
12. Redmond, P., et al., *Impact of medication reconciliation for improving transitions of care.* Cochrane Database of Systematic Reviews, 2018(8).
13. Wang, H.M., et al., *Electronic medication reconciliation in hospitals: a systematic review and meta-analysis.* European Journal of Hospital Pharmacy-Science and Practice, 2018. **25**(5): p. 245-250.
14. Meguerditchian, A.N., et al., *Medication reconciliation at admission and discharge: a time and motion study.* BMC Health Serv Res, 2013. **13**: p. 485.
15. Ebbens, M.M., et al., *Prospective Validation of a Risk Prediction Model to Identify High-Risk Patients for Medication Errors at Hospital Admission.* Ann Pharmacother, 2018. **52**(12): p. 1211-1217.
16. Hias, J., et al., *Predictors for unintentional medication reconciliation discrepancies in preadmission medication: a systematic review.* Eur J Clin Pharmacol, 2017. **73**(11): p. 1355-1377.

17. Suggett, E. and J. Marriott, *Risk Factors Associated with the Requirement for Pharmaceutical Intervention in the Hospital Setting: A Systematic Review of the Literature.* Drugs Real World Outcomes, 2016. **3**(3): p. 241-263.
18. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* J Clin Epidemiol, 2009. **62**(10): p. e1-34.
19. GA Wells, B.S., D O'Connell, J Peterson, V Welch, M Losos, P Tugwell *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* 2000.
20. Audurier, Y., et al., *Development and validation of a Score to Assess Risk of Medication Errors detected during medication reconciliation process at admission in Internal Medicine Unit: SCOREM study.* Int J Clin Pract, 2020: p. e13663.
21. Barbier, G., et al., *Securing the geriatric patient pathway: What are the risk factors for medication errors on admission?* Pharmacien Hospitalier et Clinicien, 2020. **55**(3): p. 275-281.
22. Blaine, K., et al., *Medication Order Errors at Hospital Admission Among Children With Medical Complexity.* J Patient Saf, 2020.
23. Chung, C., et al., *Medication reconciliation: Predictors of risk of unintentional medication discrepancies in the cardiology department.* Arch Cardiovasc Dis, 2019. **112**(2): p. 104-112.
24. Coffey, M., et al., *Prevalence and clinical significance of medication discrepancies at pediatric hospital admission.* Acad Pediatr, 2009. **9**(5): p. 360-365.
25. Cornu, P., et al., *Effect of medication reconciliation at hospital admission on medication discrepancies during hospitalization and at discharge for geriatric patients.* Ann Pharmacother, 2012. **46**(4): p. 484-494.
26. Damlien, L., et al., *Drug safety at admission to emergency department: an innovative model for PRIOritizing patients for MEdication Reconciliation (PRIOMER).* Eur J Emerg Med, 2015.
27. DeCourcey, D.D., et al., *Medication Reconciliation Failures in Children and Young Adults With Chronic Disease During Intensive and Intermediate Care.* Pediatr Crit Care Med, 2017. **18**(4): p. 370-377.
28. Ebbens, M.M., et al., *Risk factors for medication errors at admission in preoperatively screened patients.* Pharmacoepidemiol Drug Saf, 2018. **27**(3): p. 272-278.
29. Falconer, N., et al., *Validation of the assessment of risk tool: patient prioritisation technology for clinical pharmacist interventions.* Eur J Hosp Pharm, 2017. **24**(6): p. 320-326.
30. Gerlier, C., et al., *Identifying predictive factors leading to medication error: Optimization of medication reconciliation in an emergency care unit. [French].* Annales Francaises de Medecine d'Urgence, 2019. **9**(3): p. 156-162.
31. Gonzalez-Garcia, L., et al., *Medication reconciliation at admission to surgical departments.* J Eval Clin Pract, 2016. **22**(1): p. 20-25.
32. Guo, Q., et al., *The role of clinical pharmacist trainees in medication reconciliation process at hospital admission.* Int J Clin Pharm, 2020. **42**(2): p. 796-804.
33. Hellstrom, L.M., et al., *Errors in medication history at hospital admission: prevalence and predicting factors.* BMC Clin Pharmacol, 2012. **12**: p. 9.
34. Huber, T., et al., *Implementation of an IT-guided checklist to improve the quality of medication history records at hospital admission.* Int J Clin Pharm, 2017. **39**(6): p. 1312-1319.

35. Leguelinel-Blache, G., et al., *Impact of admission medication reconciliation performed by clinical pharmacists on medication safety.* Eur J Intern. Med, 2014. **25**(9): p. 808-814.
36. Manias, E., et al., *Medication Use Across Transition Points from the Emergency Department: Identifying Factors Associated with Medication Discrepancies.* Annals of Pharmacotherapy, 2009. **43**(11): p. 1755-1764.
37. Marinovic, I., et al., *Clinical pharmacist-led program on medication reconciliation implementation at hospital admission: experience of a single university hospital in Croatia.* Croat. Med J, 2016. **57**(6): p. 572-581.
38. Mazhar, F., et al., *Medication reconciliation errors in a tertiary care hospital in Saudi Arabia: admission discrepancies and risk factors.* Pharm Pract (Granada), 2017. **15**(1): p. 864.
39. Rentero, L., et al., *[Causes and factors associated with reconciliation errors in medical and surgical services].* Farm. Hosp, 2014. **38**(5): p. 398-404.
40. Rodriguez, V.B., et al., *Prevalence and risk factors for medication reconciliation errors during hospital admission in elderly patients.* Int J Clin Pharm, 2016. **38**(5): p. 1164-1171.
41. Salameh, L., R. Abu Farha, and I. Basheti, *Identification of medication discrepancies during hospital admission in Jordan: Prevalence and risk factors.* Saudi Pharm J, 2018. **26**(1): p. 125-132.
42. Silvestre, C.C., et al., *Risk factors for unintentional medication discrepancies at hospital admission: A matched case-control study.* Eur J Intern Med, 2017. **40**: p. e24-e25.
43. Van Der Luit, C.D., et al., *Frequency of occurrence of medication discrepancies and associated risk factors in cases of acute hospital admission.* Pharm Pract (Granada), 2018. **16**(4): p. 1301.
44. Zoni, A.C., et al., *The impact of medication reconciliation program at admission in an internal medicine department.* Eur J Intern. Med, 2012. **23**(8): p. 696-700.
45. Gomez-Martino, C.B., et al., *Medication reconciliation errors according to patient risk and type of physician prescriber identified by prescribing tool used.* Emergencias, 2017. **29**(6): p. 384-390.
46. Akram, F., et al., *Medication discrepancies and associated risk factors identified among elderly patients discharged from a tertiary hospital in Singapore.* Singapore Med J, 2015. **56**(7): p. 379-384.
47. Caleres, G., et al., *Medication Discrepancies in Discharge Summaries and Associated Risk Factors for Elderly Patients with Many Drugs.* Drugs Real World Outcomes, 2019.
48. Cornu, P., et al., *Discrepancies in medication information for the primary care physician and the geriatric patient at discharge.* Ann Pharmacother, 2012. **46**(7-8): p. 983-990.
49. Garcia-Molina, S.C., et al., *Reconciliation errors at hospital discharge in spain: Development of a predictive model.* Latin American Journal of Pharmacy, 2015. **34**(10): p. 2027-2035.
50. Geurts, M.M.E., et al., *Medication reconciliation to solve discrepancies in discharge documents after discharge from the hospital.* International Journal of Clinical Pharmacy, 2013. **35**(4): p. 600-607.
51. Grimes, T.C., et al., *Medication details documented on hospital discharge: cross-sectional observational study of factors associated with medication non-reconciliation.* Br J Clin Pharmacol, 2011. **71**(3): p. 449-457.
52. Herrero-Herrero, J.I. and J. Garcia-Aparicio, *Medication discrepancies at discharge from an internal medicine service.* Eur J Intern. Med, 2011. **22**(1): p. 43-48.

53. Osorio, S.N., et al., *Risk factors for unexplained medication discrepancies during transitions in care.* Family medicine, 2014. **46**(8): p. 587-596.

54. Ziaeian, B., et al., *Medication reconciliation accuracy and patient understanding of intended medication changes on hospital discharge.* J Gen Intern. Med, 2012. **27**(11): p. 1513-1520.

55. Breuker, C., et al., *Patients with diabetes are at high risk of serious medication errors at hospital: Interest of clinical pharmacist intervention to improve healthcare.* Eur J Intern. Med, 2016.

56. Breuker, C., et al., *Medication errors at hospital admission and discharge in Type 1 and 2 diabetes.* Diabet Med, 2017. **34**(12): p. 1742-1746.

57. Breuker, C., et al., *Medication Errors at Hospital Admission and Discharge: Risk Factors and Impact of Medication Reconciliation Process to Improve Healthcare.* J Patient Saf, 2017.

58. Dei Tos, M., C. Canova, and T. Dalla Zuanna, *Evaluation of the medication reconciliation process and classification of discrepancies at hospital admission and discharge in Italy.* Int J Clin Pharm, 2020. **42**(4): p. 1061-1072.

59. Stuijt, C.C.M., et al., *Determinants for medication reconciliation interventions on hospital admission and discharge: An observational multi-centre study.* Eur J Intern Med, 2017. **46**: p. e20-e22.

CHAPTER

3

FREQUENCY OF OCCURRENCE OF MEDICATION DISCREPANCY AND ASSOCIATED RISK FACTORS IN CASES OF ACUTE HOSPITAL ADMISSION

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ABSTRACT

Background

Medication discrepancies are a common occurrence following hospital admission and carry the potential for causing harm. However, little is known about the potential risk factors involved in medication discrepancies.

Objective

The objective of this study was to determine how frequently medication discrepancies occur and their associated risk factors, in patients hospitalized via the emergency department of the Spaarne Gasthuis Hospital, located in The Netherlands.

Methods

This retrospective observational study examines 832 hospital admissions which took place between April 1st and June 30th, 2015. Medication reconciliation was performed within 24 hours of admission and medication discrepancies were registered. The primary outcome recorded in the study was the proportion of patients experiencing one or more medication discrepancies, as verified by the physician. As a secondary outcome, the association between these discrepancies and pre-specified variables was analyzed using univariate and multivariate logistic regression.

Results

At least one medication discrepancy was found to have occurred with 97 of the 832 patients (11.7%), the most common discrepancies involving incorrect drug dose (44.9%) and omission of medication (36.4%). In the univariate analysis, age (OR=1.03 [95% CI 1.02:1.04] p<0.001) and number of pre-admission medications taken (OR=1.13 [95%CI 1.09:1.17] p<0.001) were revealed to be significantly associated with the risk of medication discrepancies. Sex, type of medical specialty, and surgical versus non-surgical specialty were found not to be significantly associated with discrepancies. In the multivariate analysis, both the number of pre-admission medications (OR=1.10 [95%CI 1.06:1.15] p<0.001) and age (OR=1.02 [95%CI 1.01:1.03] p=0.004) were independently associated with the risk of medication discrepancy.

Conclusion

Of the total number of patients, 11.7% experienced one or more medication discrepancies following admission to the hospital. Elderly patients taking multiple drugs were found to be particularly at risk.

INTRODUCTION

Up to two-thirds of all hospitalized patients will experience one or more discrepancies (differences) between the patient's medication history as determined at the point of hospital admission, and the medication prescribed during hospitalization.[1] Medication discrepancies occur most frequently at the point of hospital admission and discharge.[2,3] Between 11 and 59% of medication discrepancies are potentially harmful.[1] This constitutes a major public health burden, and one which is largely preventable.[2,4]

In the hospital setting, it is often not feasible for pharmacy professionals to perform medication reconciliation for all patients at the point of admission and discharge. To optimize quality of healthcare, it is important to identify the patient group most likely to incur medication discrepancies. Medication reconciliation for patient groups at particular risk should ideally be performed by pharmacy professionals.[5,6,7] In the Netherlands, this task is most often performed by pharmacy technicians who work under the supervision and responsibility of a pharmacist. The review by Hias *et al* examined the risk factors for medication discrepancy and identified a correlation between patient characteristics and medication discrepancies at the point of admission.[8] However, the studies reviewed mostly involved a small number of patients. These researchers also showed that the potential risk factors identified varied between different studies.[8] The number of pre-admission drugs taken was the most frequently identified risk factor for discrepancies in general, whereas age was the most frequently identified risk factor for potentially harmful discrepancies.[8] Other risk factors, such as gender, type of care before admission, number of comorbidities and type of care received prior to admission, were all associated with medication discrepancies - significantly in some studies, and non-significantly in others.[8]

Contradictory results imply that the potential risk factors for the occurrence of medication discrepancies are still not fully elucidated. Since no conclusive outcome can be found in the literature, more research is needed to identify the risk factors in this area. The aim of this study, therefore, is to determine the frequency with which medication discrepancies occur, and the associated risk factors in patients hospitalized through the emergency department of the Spaarne Gasthuis Hospital in The Netherlands. This admission group was selected, because the urgency of the patients' situation lends itself to greater risks regarding this issue.

METHODS

Study design and population

For this retrospective observational study, data were obtained from the Spaarne Gasthuis Hospital located in Haarlem, The Netherlands. Patients were included in the study if they visited the emergency department and were subsequently admitted to the hospital between April 1st and June 30th, 2015. A further inclusion criterion was the performing of medication reconciliation by the pharmacy technician, following the treating physician entering the prescribed medication on the hospital information system Epic (Verona, WI,

USA). Medication reconciliation was performed within 24 hours of admission. Available sources were reviewed in order to obtain the best possible medication history, available sources were consulted. The available medication history, as stored in the hospital information system, in cases where the patient had been previously hospitalized. The availability of medication records from the community pharmacy was also checked; in The Netherlands, medication dispensed by pharmacies is registered electronically, and this information is accessible to other healthcare professionals if the patient has granted permission for this. With these lists of medication as the starting point, semi-structured interviews with each of the patients and/or caregivers were performed, and for each drug the drug name, dosage, frequency, and route were checked. If discrepancies were identified, these were communicated to the treating physician. For patients who were re-hospitalized in the study period, only the first hospitalization was included. Patients who used no medication before admission were excluded from the study.

Data collection and monitoring

The data were collected from the hospital information system using SAP Crystal Reports (Walldorf, Germany). The extracted data were converted to Microsoft Excel version 2010 (Redmond, WA, USA). For every admission, medications prescribed prior to admission, medications prescribed on hospital admission, age, sex, and the medical specialty treating the patient, were extracted. Medications were classified according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) methodology.[9] The integrity of the data was sample-wise checked by a clinical pharmacist.

Outcome measures

The primary outcome assessed by the study was the proportion of patients experiencing one or more medication discrepancies. Medication discrepancy is defined as an inconsistency between the actual medication as detailed in Epic and the best possible medication history based on the medication reconciliation. Any inconsistency was discussed with the attending physician. Cases where the physician did not accept the proposal of the pharmacy technician and therefore did not change the prescribed medication were not included as a medication discrepancy, as the physician may have changed or stopped the medication intentionally. Four types of discrepancy were distinguished in this study: omission of medication, differing drug dose (including differing frequency of administration), restarting stopped medication, and incorrect drug (including different drug routes).

The following potential risk factors were assessed: age, sex, type of medical specialty, surgical specialty versus non-surgical, and number of drugs taken prior to admission. The secondary outcome assessed by the study was the type of medication involved in the medication discrepancy classified using the first level (anatomical main group) of the WHO ATC group, as well as the frequency of medication discrepancies as cited by this group.[9]

Data Analysis

IBM SPSS Statistics for Windows version 24 (IBM Corp, Armonk, NY) was used for the statistical analyses. Descriptive analysis was used to analyze the frequency of medication discrepancies. Univariate binary logistic regression was conducted to determine which pre-specified variables were significantly associated with the occurrence of medication discrepancies. All potential predictors with a p-value <0.05 were entered into the multivariate logistic regression analysis, adjusting for potential confounders. A p-value below 0.05 was regarded as statistically significant and 95% confidence intervals are reported.

Ethics

This study is a retrospective observational study, and as such does not the need for approval by a Medical Ethics Committee, according to the Dutch Medical Research Involving Human Subjects Act. All patients received usual care and data were gathered retrospectively and processed anonymously, according to privacy legislation.

RESULTS

During the study period, a total of 999 medication reconciliations were performed, all occurring within 24 hours of hospital admission. Sixty-three medication reconciliation interviews were excluded on account of the patients being re-hospitalized within the study period. A further 104 patients were excluded because they did not use medication before admission. Thus, 832 patients were included in the analyses (Table 1).

In 97 of the 832 patients, at least one medication discrepancy was detected (11.7%). A total of 176 medication discrepancies were identified in these 97 patients, which gives a frequency of 0.21 discrepancies per admission and 1.8 discrepancies per admission with at least one medication discrepancy. The prescribing of an incorrect drug dose was found to be the most common discrepancy type, followed by the omission of medication (Table 2). Drugs most frequently involved in medication discrepancies pertained to the ATC groups 'Systemic hormonal preparations', 'Cardiovascular system' and 'Sensory organs' (Table 3).

The univariate logistic regression analysis showed that age (OR=1.03 [95%CI 1.02:1.04] P<0.001) was significantly associated with the risk of medication discrepancy (Table 4). Patients younger than 18 years had the lowest risk and the risk increased in patients of 66 years and above. Furthermore, a significant association between the number of medications taken prior to admission (OR=1.13 [95%CI 1.09:1.17] p<0.001) and the risk of medication discrepancies, was found. In patients using less than seven medications, the frequency of one or more medication discrepancies at admission was 0.05, while in patients using seven or more medications the frequency was 0.24. No significant association was found with sex and medical specialty. In the multivariate analysis, the number of pre-admission medications taken (OR=1.10 [95%CI 1.06:1.15] p<0.001) and age (OR=1.02 [95%CI 1.01:1.03] p=0.004) were statistically significantly associated with the frequency of medication discrepancy.

Table 1. Baseline characteristics (n = 832)

Characteristics	
Sex, n (%)	
Male	387 (46.5)
Age in years, mean (SD[a])	63.5 (23.5)
Age categories, n (%)	
≤18	60 (7.2)
19-45	94 (11.3)
46-65	198 (23.8)
66-75	157 (18.9)
76-85	204 (24.5)
>85	119 (14.3)
Medical specialty, n (%)	
Gastroenterology	88 (10.6)
Geriatrics	116 (13.9)
Internal	203 (24.4)
Neurology	63 (7.6)
Pediatrics	45 (5.4)
Pulmonology	101 (12.1)
Surgical	187 (22.5)
Other[b]	29 (3.5)
Number of medications taken prior to admission, mean (SD)	6.9 (4.9)
minimum	1
maximum	26

[a] SD = standard deviation

[b] Others; includes urology, gynecology, dental specialisms, cardiology, otorhinolaryngology

Table 2. Type of medication discrepancy (n=176)

Type of discrepancy	n (%)
Omission of medication	64 (36.4)
Differing drug dose	79 (44.9)
Restarting stopped medication	14 (8.0)
Incorrect drug	19 (10.8)

DISCUSSION

In approximately one in nine acutely admitted patients at least one medication discrepancy was identified during medication reconciliation. Independent risk factors for medication discrepancy were identified as age and the number of pre-admission medications taken. The prescribing of an incorrect drug dose was the most common discrepancy, followed

Table 3. Number of prescribed medications and discrepancies per ATC-group.

ATC-code	Number of prescribed medications	Number of discrepancies (n=176)	Frequency of discrepancies per ATC-group (%)
A: Alimentary tract and metabolism	1373	45	3.3
B: Blood and blood forming organs	532	4	0.8
C: Cardiovascular system	1284	51	4.0
D: Dermatologicals	130	5	3.8
G: Genito-urinary system and sex hormones	109	4	3.7
H: Systemic hormonal preparations[a]	170	9	5.3
J: Anti-infective for systemic use	130	1	0.8
L: Antineoplastic and immunomodulating agents	55	0	0.0
M: Musculo-skeletal system	210	4	1.9
N: Nervous system	944	25	2.6
R: Respiratory system	534	17	3.2
S: Sensory organs	110	10	9.1
Others	44	1	2.3

[a] excluding sex hormones and insulin's

by the omission of medication. In our study, medication discrepancies were excluded if the physician did not change the discrepancy following notification.

A study by Allende Bandrés *et al.* differentiated medication discrepancy justified by a pharmacist and found a frequency of 1.8 medication discrepancies per admission with at least one medication discrepancy, which is in line with the current study's findings.[10] Cornu *et al*. identified 279 medication discrepancies which were accepted in 163 patients (giving a frequency of 1.7, as compared to 1.8 in the current study.[11] The study also revealed a frequency of 1.4 medication discrepancies per admission, which is higher than the current study's findings, of a frequency of 0.21. However, there are substantial differences in methodology between the current study and that of Cornu *et al*. – for example, in the latter study, only patients aged 65 years and older were included. The average age in the study population assessed by Cornu *et al*. was therefore older than in the current study (83.7 versus 63.5 years) and the study population used more medications prior to admission (7.2 versus 6.9). Since the current study found an association between increasing age and higher numbers of pre-admission medications, and the occurrence of medication discrepancies, it can be assumed that those particular risk factors contributed to the relatively high frequency of discrepancies reported by Cornu *et al*.

To the best of the author´s knowledge, this is the first study to assess the frequency of occurrence of medication discrepancies according to WHO ATC group. Patients using medications from the ATC groups "Systemic hormonal preparations", "Cardiovascular system" and "Sensory organs" were found to be at greater risk. Four previous studies

Table 4. Univariate and multivariate analyses: possible risk factors for medication discrepancies

Variable	All admissions (n=832)	Medication discrepancies/ admission (n=97) (%)[a]	Odds ratio [95%CI]	Adjusted Odds ratio [95%CI]
Sex				-
Female	445	51 (11.5)	1 (ref)	
Male	387	46 (11.9)	1.04 [0.68:1.59]	
Age, years (SD)	63.5 (23.5)	74.0 (14.3)	1.03 [1.02:1.04] *	1.02 [1.01:1.03] *
Age categories, in years				
≤18	60	1 (1.7)	0.51 [0.05:5.06]	-
19-45	94	3 (3.2)	1 (ref)	
46-65	198	13 (6.6)	2.13 [0.59:7.67]	
66-75	157	29 (18.5)	6.87 [2.03:23.25] *	
76-85	204	34 (16.7)	6.07 [1.81:20.30] *	
>86	119	17 (14.3)	5.06 [1.44:17.81] *	
Number of medications taken prior to admission (SD)	6.9 (4.9)	9.9 (4.1)	1.13 [1.09:1.17] *	1.10 [1.06:1.15] *
Type of medical specialty, no				
Non-surgical	620	74 (11.9)	1 (ref)	-
Surgical	212	23 (10.8)	0.90 [0.55:1.48]	
Medical specialty				
Gastroenterology	88	8 (9.1)	0.56 [0.24:1.26]	-
Geriatrics	116	16 (13.8)	0.89 [0.46:1.70]	
Internal	203	31 (15.3)	1 (ref)	
Neurology	63	5 (7.9)	0.48 [0.18:1.29]	
Pediatrics	45	1 (2.2)	0.13 [0.02:0.95] *	
Pulmonology	101	12 (11.9)	0.75 [0.37:1.53]	
Surgical	187	22 (11.8)	0.74 [0.41:1.33]	
Other[b]	29	2 (6.9)	0.41 [0.09:1.82]	

[a] percentage of the number of admissions; b 'Other' includes urology, gynecology, dental specialisms, cardiology, otorhinolaryngology

* statistically significant at $p<0.05$

have divided up medication discrepancies according to drug class.[8] The most common discrepancy that was found in the current study was incorrect drug dose. This is not consistent with earlier studies, in which omissions constituted the most common discrepancy found.[1] This difference in findings may be explained by differences in methodology. Omitting to prescribe a drug might be intentional, while in the current study only medication discrepancies that were accepted by the physician were included.

The number of pre-admission medications taken was the most frequently identified risk factor for medication discrepancy in the review conducted by Hias et al.[8] The odds ratio for each additional medication varied from 1.09 to 1.47 in these studies, compared

with 1.13 in the current study.[8] Age was also investigated as a risk factor, but the literature revealed no conclusive outcome.[8] Studies inferred that increasing age is associated with the frequency of medication discrepancy did not always adjust for potential confounders such as underlying diseases.[1-2, 10-11] The results detailed are similar to those of the current study. Hias et al. showed that 5 out of 24 studies found an association between sex and the frequency of medication discrepancies.[8] Our results showed no association between sex and the number of medication discrepancy, in line with other studies.[8]

Our study has both strengths and limitations. Firstly, this study is noteworthy in that, to the best of our knowledge, it is the largest study to date examining the risk factors for medication discrepancy in acutely admitted patients. Secondly, this study excluded discrepancies that were not accepted by the physician following notification. Thirdly, this study analyzed the medication discrepancies with reference to ATC grouping in order to assess whether some medications were more often involved in discrepancies than others. A potential limitation of the study is that we did not include medication discrepancies that remained unchanged by the physician after notification. It was assumed that, in such cases, the discrepancies were intentional rather than being in error. It is possible that this resulted in a lower frequency of medication discrepancies in our study, compared to earlier studies. Secondly, this study did not differentiate between discrepancies that were not clinically relevant and those that were. Thirdly, this study was performed in just one hospital, potentially limiting the generalizability of the results.

This study suggests the importance of performing medication reconciliation. It confirms that patient age and the number of preadmission medications taken are independent risk factors for medication discrepancy in acutely admitted patients and identifies various drug groups as being particularly susceptible. It is recommended that medication reconciliation to be conducted prior to prescription, to mitigate the possibility of medication errors. Future research might examine how to better differentiate between accepted and not accepted medication discrepancies and determine the clinical relevance of this issue.

CONCLUSION

To conclude, approximately one in nine patients acutely admitted to the hospital were found to have experienced one or more medication discrepancies. Patients using medications from the ATC groups "Systemic hormonal preparations", "Cardiovascular system" and "Sensory organs" were most at risk in this regard. Both increasing age and a higher number of pre-admission medications were found to be potential risk factors for medication discrepancies during admission. It is suggested that consideration should be given to deploying pharmacy professionals in the performing of the medication reconciliation for these high-risk patients, in order to reduce the occurrence of medication discrepancy following hospital admission.

REFERENCES

1. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ. 2005 Aug 30;173(5):510-5.
2. Hellström LM, Bondesson Å, Höglund P, Eriksson T. Errors in medication history at hospital admission: prevalence and predicting factors. BMC Clin Pharmacol. 2012 Apr 3;12:9.
3. Vira T, Colquhoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. Qual Saf Health Care. 2006 Apr;15(2):122-6.
4. Kraus SK, Sen S, Murphy M, Pontiggia L. Impact of a pharmacy technician-centered medication reconciliation program on medication discrepancies and implementation of recommendations. Pharm Pract (Granada). 2017 Apr-Jun;15(2):901.
5. Phatak A, Prusi R, Ward B, Hansen LO, Williams MV, Vetter E, Chapman N, Postelnick M. Impact of pharmacist involvement in the transitional care of high-risk patients through medication reconciliation, medication education, and postdischarge call-backs (IPITCH Study). J Hosp Med. 2016 Jan;11(1):39-44.
6. Li J, Young R, Williams MV. Optimizing transitions of care to reduce rehospitalizations. Cleve Clin J Med. 2014 May;81(5):312-20.
7. Mekonnen AB, McLachlan AJ, Brien JA. Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis. J Clin Pharm Ther. 2016 Apr;41(2):128-44.
8. Hias J, Van der Linden L, Spriet I, Vanbrabant P, Willems L, Tournoy J, De Winter S. Predictors for unintentional medication reconciliation discrepancies in preadmission medication: a systematic review. Eur J Clin Pharmacol. 2017 Nov;73(11):1355-1377.
9. WHO Collaborating Centre for Drug Statistics Methodology. Complete ATC index. https://www.whocc.no/atc_ddd_index/, accessed at September 30th 2017
10. Allende Bandrés MÁ, Arenere Mendoza M, Gutiérrez Nicolás F, Calleja Hernández MÁ, Ruiz La Iglesia F. Pharmacist-led medication reconciliation to reduce discrepancies in transitions of care in Spain. Int J Clin Pharm. 2013 Dec;35(6):1083-90.
11. Cornu P, Steurbaut S, Leysen T, De Baere E, Ligneel C, Mets T, Dupont AG. Effect of medication reconciliation at hospital admission on medication discrepancies during hospitalization and at discharge for geriatric patients. Ann Pharmacother. 2012 Apr;46(4):484-94.

CHAPTER

4

RISK FACTORS FOR MEDICATION ERRORS AT ADMISSION IN PREOPERATIVELY SCREENED PATIENTS

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ABSTRACT

Background

Preoperative screening (POS) may help to reduce medication errors at admission (MEA). However, due to the time window between POS and hospital admission unintentional medication discrepancies may still occur and thus a second medication reconciliation at hospital admission can be necessary. Insight into potential risk factors associated with these discrepancies, would be helpful to focus the second medication reconciliation on high risk patients.

Objective

To determine the proportion of POS patients with MEA and to identify risk factors for MEA.

Methods

This single-center observational cross-sectional study included elective surgical patients between October 26th and December 18th 2015. Main exclusion criteria were age younger than 18 years and daycare admissions. Medication reconciliation took place at the POS and was repeated within 30 hours of admission. Unintended discrepancies between the first and second medication reconciliation were defined as MEA. The primary outcome was the proportion of patients with one or more MEA. The association of this outcome with potential risk factors was analyzed using multivariate logistic regression analysis.

Results

Of the 183 included patients 60 (32.8%) patients had at least one MEA. In a multivariate model number of medications at POS [adjusted odds ratio 1.16 (95%-confidence interval 1.04-1.30)], and respiratory disease [4.25 (1.52-11.83)] were significantly associated with MEA.

Conclusion

In one third of preoperatively screened patients a MEA was found. The number of medications and respiratory comorbidities are risk factors for MEA in preoperatively screened patients.

INTRODUCTION

Medication errors during hospital admission are common and potentially clinically relevant. Up to 67% of patients have at least one medication history error at admission.[1] To reduce medication errors it is essential to perform medication reconciliation at hospital admission. Medication reconciliation has been shown to reduce unintentional medication discrepancies with 66%.[2] At the day of admission for elective surgery, it is impracticable to reconcile medication before surgery because of the limited time between admission and surgery. To overcome this problem, the majority of medication reconciliation in elective patients in Dutch hospitals is performed at the ambulatory preoperative screening (POS) clinic. At the POS the anaesthesiologists screen a patient's medical condition and history to determine which kind of anaesthesia will be used and whether the surgery can be performed safely. A disadvantage of medication verification at the time of preoperative screening is the time between medication reconciliation and admission. This time may vary from one day to three months. Changes in medication in this period will lead to unintentional medication discrepancies at admission.[3] So far, there are no studies on the number of unintentional medication discrepancies that may occur at the time of hospital admission after previous preoperative medication reconciliation.

In addition, the risk factors that are associated with these discrepancies are unknown. In general, polypharmacy and age are well known risk factors associated with unintentional medication discrepancies.[4-9] Multiple comorbidities have also been shown to increase the risk of medication discrepancies.[4, 8] However, it is unknown whether these risk factors for medication discrepancies also apply to medication discrepancies occurring at hospital admission after previous medication reconciliation at the POS. Yet, knowledge of these risk factors could enable selection of patients who would not need a second medication reconciliation at hospital admission. This would increase the efficiency of the medication reconciliation process and reduce work load and costs. On the other hand, patients at high risk will receive better care if we are able to select these patients.

Therefore, the objective of this study is to determine the proportion of preoperatively screened patients in which medication errors at admission were found, and to identify risk factors leading to these errors.

METHODS

Design

A prospective observational cross-sectional study was carried out in the Zaans Medical Centre, Zaandam, The Netherlands. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center in Leiden and by the board of directors of the Zaans Medical Centre. Patients were included when written informed consent was given. At the POS patients are screened by anesthesiologists in order to assess whether the patient is suitable to receive anesthesia. Medication reconciliation was performed by the pharmacy technician according to usual care. The goal of the medication reconciliation

was to acquire the best home medication use. Medication reconciliation consisted of a standardized medication interview with the patient performed by the pharmacy technician. In this medication interview the medication record of the community pharmacy was used to verify actual medication use with the patient. In case the patient could not answer these questions completely, the accompanying caregiver was interviewed as well. In case the patient could not answer the questions and did not have an accompanying caregiver who could, the patient was not included in the study. Furthermore, patients are routinely asked to report any change in medication if this occurred in the period between the POS and admission. When reported, the pharmacy technician processes this in the patient record. Within 30 hours of hospital admission the medication reconciliation was repeated by a pharmacy technician using the same procedure as used for medication reconciliation at the POS. The medication reconciliation took place either pre- or post-operative. The peri-operative medication use was outside the scope of this study.

Study population

All patients who attended the POS between October 26th and December 18th 2015 were approached to participate in the study. Exclusion criteria were: age younger than 18 years, hospital admission of less than 24 hours, no medication reconciliation within 30 hours of admission or physical/mental inability to give informed consent.

Data collection

General patient and medical data were collected from the electronic patient record: age, sex, number of medications, comorbidities (hypertension, cardiovascular disease, respiratory disease, diabetes mellitus, thyroid disease, cerebral vascular accident, kidney disease, epilepsy, thrombosis/embolism), quality score of the medication reconciliation interview (good, sufficient or insufficient), medical specialty and ASA score. The ASA score stands for American Society of Anesthesiologists physical status classification and is used to identify the physical status before surgery.[10] The included comorbidities are routinely obtained from a patient questionnaire at the POS.

The score of the medication reconciliation interview was given by the pharmacy technician as an indicator for the quality of the interview. There are three options for the pharmacy technician to score the quality of the interview: good, sufficient, or insufficient. The pharmacy technician scored good if the medication reconciliation gives an accurate complete overview of the medication, sufficient when the medication reconciliation produced the most important medication but some questions remained open, and insufficient when the medication reconciliation did not result in a complete overview of the medication. The patient was asked about his living situation, educational level and to perform the Short Assessment of Health Literacy – Dutch (SAHL-D)[11] at the moment of inclusion at the POS. The SAHL-D is a screening tool consisting of 33 health related terms to predict the health literacy of a patient. The result of the SAHL-D is a score between 0 and 66, with the highest score standing for very adequate health

literacy and the lowest score for inadequate health literacy. There was no cut-off point chosen for adequate versus inadequate health literacy: the score was included as a continuous variable.

The person with whom the medication reconciliation at the POS was performed (patient or accompanying caregiver), was also registered. A second medication reconciliation was performed within 30 hours of admission. After this second medication reconciliation the time between POS and admission was registered and the discrepancies between the first and second medication reconciliation were noted, and if necessary discussed with the attending physician. Furthermore the type of medication involved in the discrepancy using the Anatomic Therapeutic Chemical (ATC) code[12] was noted. Using the ATC classification enables the grouping of similar medication, making it possible to identify such a group as a potential risk factor.

Classification of medication errors

A medication error at admission (MEA) was defined as an unintended discrepancy between medication at the POS and admission. Whether the discrepancy was unintended was assessed by an expert team composed of an internist acute medicine (MAD), a hospital pharmacist (EW) and a hospital pharmacist trainee (ME). To determine if a discrepancy was unintended the information from both medication reconciliation interviews and the electronic patient record was used. The screening was performed independently from each other. When disagreement existed after the first screening, consensus was reached. Three types of medication errors were defined: omission of a pre-admission prescription medication, wrongful start of medication (commission), and unintended change in dose or frequency. If a discrepancy was assessed as a medication error at admission the potential harm of the error was determined by the expert team using the method described by *Gleason*[6]. *Gleason et al* describe three categories of potential harm: No potential harm, potential for increased monitoring or intervention to preclude harm, and potential harm.

Outcome

The primary outcome was the proportion of patients with one or more medication errors at hospital admission. The association of this outcome with potential risk factors (age, sex, number of medications, ASA score or nine comorbidities, time between POS and admission, health literacy or educational level, and living situation)[4-9] was analyzed as a secondary outcome.

Other secondary outcomes were the type and clinical relevance of the MEA, and the type of medication involved in MEA's.

Data monitoring

Data monitoring was performed by verifying data, imported into the database, by a second person. Furthermore, in the data analysis, data were checked for missing and non-existing values.

Data analysis

All data were collected in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA). Data analysis was carried out using IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY). The sample size calculation was based on the incidence from a pilot study of 50% unintentional medication discrepancies, alpha of 0.05 and the assumption that in the final multivariate logistic regression model not more than ten independent variables would be included[13]. Given these assumptions a sample size of 200 patients was calculated.

First, the prevalence was calculated by dividing the number of patients with one or more MEA's by the total number of patients. Second, the association of all potential risk factors with the primary outcome was analyzed using univariate logistic regression. If the p-value was ≤ 0.20, the parameter was included in the multivariate logistic regression model. Parameters that were correlated (Pearson correlation > 0.5) were not included in the same model. A stepwise backwards approach was used for the multivariate model. Variables were included in the multivariate model if they contributed significantly to the model. (Adjusted) odds ratio's (OR) and 95% confidence intervals (95% CI) were reported.

RESULTS

In a period of 6 weeks 1208 patients were screened for eligibility at the preoperative screening, of which 213 patients were initially included. In 30 of these 213 patients no medication reconciliation interview was performed at admission, so the final study population comprised 183 patients (Figure 1). Table 1 shows the baseline characteristics of these patients.

Of the 183 included patients 60 (32.8%) had at least one MEA. These MEA's were classified by the expert team. In 10% of the discrepancies discussion was needed to reach consensus. Patient characteristics were included in a univariate logistic regression (Table 2).

ASA score and comorbidities were correlated and therefore not included in the same multivariate model. The results of the multivariate logistic regression are presented in Table 3. The first model included ASA score as a summary of individual comorbidities. In this multivariate model only number of medications at the POS remained statistically significant (OR 1.24; 95% CI 1.12-1.37). A second multivariate model was computed where instead of the ASA score the individual comorbidities listed in Table 2, with a p-value below 0.20, were included. In this second multivariate analysis number of medications (OR 1.16; 95% CI 1.04-1.30) and respiratory comorbidities (OR 4.25 95% CI 1.52-11.83) were significantly contributing to the model, adjusted odds ratios are shown in Table 3. Although diabetes mellitus and cardiovascular comorbidity were significantly associated with MEA in the univariate model, they were not significant in the multivariate model. Cardiovascular comorbidity did influence the model significantly and therefore is included in the second multivariate model.

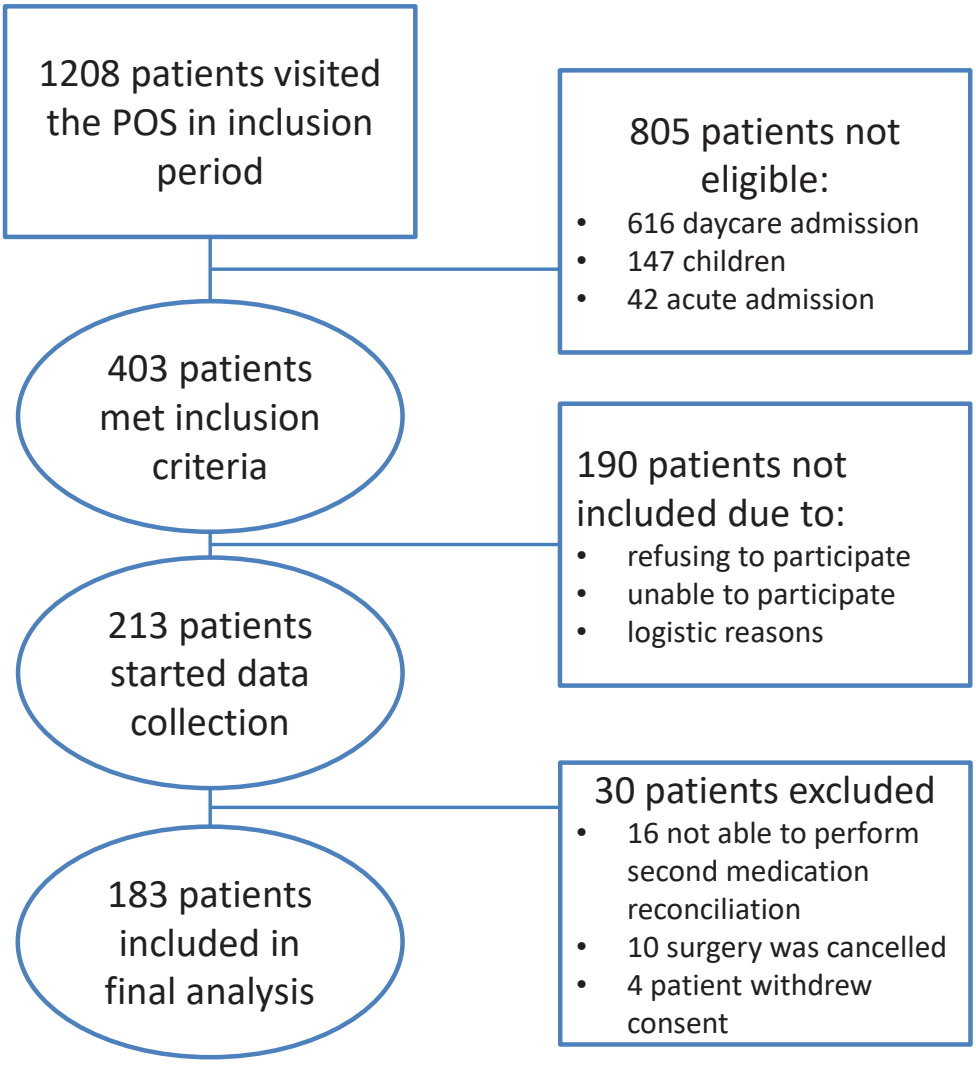

Figure 1. Patient inclusion

A total of 89 MEA were identified in the 60 patients with one or more MEA. Of these MEA 67 (75.2%) were assessed by the expert panel as causing no potential harm, 21 (23.6%) as having potential for increased monitoring or intervention to preclude harm and 1 (1.1%) as having potential harm. In total 17 (9.3%) patients had at least one MEA with potentially harmful consequences. The type of error was an omission in 34 cases, a commission in 33 cases, and changes in frequency or dose in 22 cases. The medication classes most frequently involved in the MEA were alimentary tract and metabolism (19%), respiratory system (17%), dermatologic medication (11%), and nervous system (11%).

Table 1. Patient characteristics (n=183)

		Patients with MEA (n=60)	Patients without MEA (n=123)	Total (n=183)
Age (mean ± SD)		62.5 ± 16.1	61.4 ± 16.5	61.8 ± 16.3
Sex men, n (%)		25 (42%)	52 (42%)	77 (42%)
Number of medications at screening (mean ± SD)		5.2 ± 3.7	2.8 ± 3.1	3.7 ± 3.5
ASA score[1] (mean ± SD)		2.1 ± 0.67	1.7 ± 0.67	1.8 ± 0.69
Time in days between preoperative screening and admission.	1-14 (%)	19 (32%)	32 (26%)	51 (28%)
	15-27 (%)	15 (25%)	28 (23%)	43 (23%)
	28-48 (%)	15 (25%)	29 (24%)	44 (24%)
	>48 (%)	11 (18%)	34 (28%)	45 (25%)
SAHL-D[2] (mean ± SD)		43.4 ± 16.1	44.9 ± 15.1	44.4 ± 15.4
Living situation				
Independent (%)		52 (87%)	109 (89%)	161 (87%)
Family caregiving (%)		3 (5%)	7 (6%)	10 (5%)
Professional home care (%)		5 (8%)	7 (6%)	12 (7%)
Telephone call to report change in medication		1 (2%)	6 (5%)	7 (4%)
Level of education				
Primary school (%)		5 (8%)	9 (7%)	14 (8%)
Secondary school (%)		15 (25%)	28 (23%)	43 (23%)
Selective secondary school (%)		1 (2%)	8 (7%)	9 (5%)
Vocational education (%)		27 (45%)	45 (37%)	72 (39%)
University of applied sciences (%)		11 (18%)	24 (20%)	35 (19%)
University (%)		1 (2%)	9 (7%)	10 (5%)
Quality score medication reconciliation interview				
Good (%)		48 (80%)	111 (90%)	159 (87%)
Sufficient (%)		12 (20%)	12 (10%)	24 (13%)
Insufficient (%)		0 (0%)	0 (0%)	0 (0%)
Hypertension (%)		20 (33%)	35 (29%)	55 (30%)
Cardiovascular disease (%)		13 (22%)	9 (7%)	22 (12%)
Respirator disease (%)		15 (25%)	7 (6%)	22 (12%)
Diabetes (%)		11 (18%)	8 (7%)	19 (10%)
Thyroid disease (%)		8 (13%)	9 (7%)	17 (9%)
Cerebral vascular accident (%)		6 (10%)	4 (3%)	10 (5%)
Kidney disease (%)		1 (2%)	5 (4%)	6 (3%)
Epilepsy (%)		2 (3%)	0 (0%)	2 (1%)
Thrombose/embolism (%)		1 (2%)	3 (2%)	4 (2%)

[1] Physical status classification for assessing fitness before surgery by the American Society of Anesthesiologists.
[2] Short assessment of health literacy in Dutch

Table 2. All parameters included in logistic regression

Parameter	Univariate Odds Ratio (95%-confidence interval)
Age[1]	1.00 (0.99-1.02)[#]
Sex[2]	1.03 (0.55-1.92)
Number of medications at preoperative screening[1]	1.24 (1.12-1.37)[*]
ASA score[1]	2.22 (1.38-3.57)[*]
Time in days between preoperative screening and admission[3]	0.84 (0.64-1.10)
Health literacy[1]	0.99 (0.97-1.01)
Education level[1]	0.95 (0.81-1.13)
Living situation[1]	1.17 (0.67-2.05)
Hypertension[2]	1.26 (0.65-2.44)
Cardiovascular disease[2]	3.50 (1.40-8.75)[*]
Respiratory disease[2]	5.52 (2.11-14.44)[*]
Diabetes mellitus[2]	3.22 (1.22-8.51)[*]
Thyroid disease[2]	1.95 (0.71-5.34)[#]
Cerebral vascular accident[2]	3.31 (0.90-12.20)[#]
Renal disease[2]	0.40 (0.46-3.50)
Epilepsy[2]	Not enough patients
History of thrombosis[2]	0.68 (0.07-6.66)
Conversation score preoperative screening[1]	0.43 (0.18-1.03)[#]

[1]Included in the logistic regression model as continuous variable.
[2]Included in the logistic regression model as categorical variable were the lowest value (or not having a disease) was the reference group.
[3] Included in the logistic regression model as categorical variable in 4 equal groups.
[*] p-value <0.05
[#] p-value <0.20

DISCUSSION

The proportion of patients with MEA's after being preoperatively screened was 33%. This percentage is relatively high compared to some studies[2, 14], and is comparable to an earlier study in preoperative patients[15]. Number of medications, and respiratory comorbidities were associated with a higher risk of MEA's. In 9.3% of patients the MEA had potentially harmful consequences.

Consistent with the findings in this study number of medications is widely found as risk factor for medication errors in transitions of care[4, 6, 8, 14, 16-19] Number of medications is a very obvious risk factor for medication errors, the more medication a patient uses, the higher the risk of errors.

Multiple comorbidities have been found as risk factor for medication errors consistent with the findings in our study[4, 8, 17]. A possible explanation for a comorbidity as an independent risk factor is that comorbidities provide varied pharmacotherapy which makes the medication more complex and more difficult to transfer in transitions of care. Earlier studies only examined multiple comorbidities as a risk factor, not the individual

Table 3. Multivariate logistic regression

Parameter included in multivariate model	Multivariate model 1 adjusted Odds Ratio (95%-confidence interval)	Adjusted for	Multivariate model 2 adjusted Odds Ratio (95%-confidence interval)	Adjusted for
Age[1]	N/A		N/A	
Number of medications at preoperative screening[1]	1.24 (1.12-1.37)*	none	1.16 (1.04-1.30)*	cardiovascular disease and respiratory disease
ASA score[2]	N/A		Not tested	
Cardiovascular disease[3]	Not tested		2.48 (0.89-6.86)	number of medications at preoperative screening, and respiratory disease
Respiratory disease[3]	Not tested		4.25 (1.52-11.83)*	number of medications at preoperative screening, and cardiovascular disease
Diabetes mellitus[3]	Not tested		N/A	
Thyroid disease[3]	Not tested		N/A	
Cerebral vascular accident[3]	Not tested		N/A	
Conversation score preoperative screening[1]	N/A		N/A	

[1]Included in both multivariate models
[2]Included in the first multivariate model
[3] Included in the second multivariate model
* p-value <0.05
N/A Not applicable

comorbidities[4, 17]. Respiratory comorbidity as a risk factor can be explained by the type of medication used for respiratory diseases: inhalation medication and their devices are easily transferred incompletely (for example, metered dose inhaler unintendedly switched to dry powder inhaler).

Age is also often found as a risk factor for medication errors. In our study it is not. This may be explained by the high correlation between age and number of medications where number of medications is already included in the model.[20] Another explanation could be the relatively young population in this study compared to other studies.[2]

Time between POS and admission is not significantly associated with MEA. This is not what we expected, because logically the more time between POS and admission, the higher the risk of changes in medication. This is the first study to evaluate time as a parameter, thus more research is necessary to confirm this finding.

Educational level and health literacy did not significantly influence the risk of a MEA conflicting with earlier results of Osorio et al.[21]

In literature the type of MEA is most often omission.[1, 14] The higher prevalence of commissions seen in this study can be explained by the fact that this study repeats medication reconciliation, therefore the home medication is known and changes in starting as well as stopping medication can occur. Therefore the prevalence of omission and commission are the same in this study.

In this study we found most errors in the drug classes' alimentary tract and metabolism; respiratory system; dermatologic medication and nervous system. Earlier studies also found sedatives and analgesics (nervous system medication) as most frequently involved drug class in medication history errors.[1] The other drug classes are not associated with medication errors in earlier studies.

Several limitations need to be discussed. First, this study is performed in only one medical centre in the Netherlands. To study whether these risk factors can be generalized to all the hospitals in the Netherlands the study should be repeated in another hospital preferably with a different patient population. Second, although we searched the literature for potential risk factors, it is possible that unknown risk factors are not included in this study. This is supported by the fit of the logistic regression model which can predict 74% of the outcomes correctly, 26% is still not explained by this model. Third, the study may be underpowered to detect whether some parameters were statistical significant. Furthermore the expert group that classified the medication errors did not include an anaesthesiologist or surgeon, however the patient record was available to verify the intention of medication changes.

This is the first study that investigates the occurrence of medication errors at admission in preoperatively screened patients. A strength of this study is that patients from all specialties with an overnight admission for elective surgery were included and therefore the results apply to all elective surgical patients in the Zaans Medical Centre. Another strength is the fact that the data that are used are routinely collected in usual care, therefore high risk patients are easily identified for a follow-up intervention study.

As the frequency of MEA is high even after preoperative screening, further research to establish what intervention is successful in reducing MEA's is necessary.

In future research the risk factors, number of medications and respiratory comorbidity, found in this study can be used to perform medication reconciliation at admission in high risk patients. This can be useful if the capacity of the pharmacy technicians is not sufficient to perform medication reconciliation at admission in every patient. However future research is necessary to investigate if these risk factors also apply to other populations in different hospital settings.

CONCLUSION

After preoperative screening, 33% of patients have one or more medication error at hospital admission. Number of medications and respiratory comorbidities are associated with a higher risk of MEA. Future research is necessary to investigate if the risk factors found in this single-center study also apply to other populations.

REFERENCES

1. Tam VC, Knowles SR, Cornish PL, et al., Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. *CMAJ*, 2005;173(5):510-515.
2. Mekonnen AB, McLachlan AJ, Brien JA, Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis. *J Clin Pharm Ther*, 2016;41(2):128-144.
3. van den Bemt PM, van den Broek S, van Nunen AK, Harbers JB, Lenderink AW, Medication reconciliation performed by pharmacy technicians at the time of preoperative screening. *Ann Pharmacother*, 2009;43(5):868-74.
4. Baena Parejo MI, Juanes Borrego AM, Altimiras RJ, et al., Medication list assessment in Spanish hospital emergency departments. *J Emerg Med*, 2015;48(4):416-423.
5. Cornish PL, Knowles SR, Marchesano R, et al., Unintended medication discrepancies at the time of hospital admission. *Arch Intern. Med*, 2005;165(4):424-429.
6. Gleason KM, McDaniel MR, Feinglass J, et al., Results of the Medications at Transitions and Clinical Handoffs (MATCH) study: an analysis of medication reconciliation errors and risk factors at hospital admission. *J Gen Intern. Med*, 2010;25(5):441-447.
7. Leguelinel-Blache G, Arnaud F, Bouvet S, et al., Impact of admission medication reconciliation performed by clinical pharmacists on medication safety. *Eur J Intern. Med*, 2014;25(9):808-814.
8. Mueller SK, Sponsler KC, Kripalani S, Schnipper JL, Hospital-based medication reconciliation practices: a systematic review. *Arch Intern Med*, 2012;172(14):1057-69.
9. Salanitro AH, Osborn CY, Schnipper JL, et al., Effect of Patient- and Medication-Related Factors on Inpatient Medication Reconciliation Errors. *Journal of General Internal Medicine*, 2012;27(8):924-932.
10. Owens WD, Felts JA, Spitznagel EL, Jr., ASA physical status classifications: a study of consistency of ratings. *Anesthesiology*, 1978;49(4):239-43.
11. Pander Maat H, Essink-Bot ML, Leenaars KE, Fransen MP, A short assessment of health literacy (SAHL) in the Netherlands. *BMC Public Health*, 2014;14:990.
12. WHO Collaborating Centre for Drug Statistics Methodology. Complete ATC index 2016. http://www.whocc.no/atcddd/. Updated December 19, 2016 Accessed September 25, 2017;
13. Ebbens MM, Bouwman N, Wesselink EJ, Medicatieverificatie bij geplande opnames, is het medicatieoverzicht bij opname compleet? . *Nederlands Platform voor Farmaceutisch Onderzoek*, 2016;1:a1620.
14. Kwan Y, Fernandes OA, Nagge JJ, et al., Pharmacist medication assessments in a surgical preadmission clinic. *Arch Intern. Med*, 2007;167(10):1034-1040.
15. Hale AR, Coombes ID, Stokes J, et al., Perioperative medication management: expanding the role of the preadmission clinic pharmacist in a single centre, randomised controlled trial of collaborative prescribing. *BMJ Open*, 2013;3(7).
16. Akram F, Huggan PJ, Lim V, et al., Medication discrepancies and associated risk factors identified among elderly patients discharged from a tertiary hospital in Singapore. *Singapore Med J*, 2015;56(7):379-384.

17. Belda-Rustarazo S, Cantero-Hinojosa J, Salmeron-Garcia A, et al., Medication reconciliation at admission and discharge: an analysis of prevalence and associated risk factors. *Int J Clin Pract*, 2015;69(11):1268-1274.

18. Gonzalez-Garcia L, Salmeron-Garcia A, Garcia-Lirola M, et al., Medication reconciliation at admission to surgical departments. *J Eval Clin Pract*, 2016;22(1):20-25.

19. Kwan Y, Fernandes OA, Nagge JJ, et al., Pharmacist medication assessments in a surgical preadmission clinic. *Arch Intern Med*, 2007;167(10):1034-40.

20. Bjerrum L, Sogaard J, Hallas J, Kragstrup J, Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. *Eur J Clin Pharmacol*, 1998;54(3):197-202.

21. Osorio SN, Abramson E, Pfoh ER, et al., Risk factors for unexplained medication discrepancies during transitions in care. *Family medicine*, 2014;46(8):587-596.

CHAPTER

5

PROSPECTIVE VALIDATION OF A RISK PREDICTION MODEL TO IDENTIFY HIGH-RISK PATIENTS FOR MEDICATION ERRORS AT HOSPITAL ADMISSION

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ABSTRACT

Background

Pharmacy led medication reconciliation in elective surgery patients is often performed at the preoperative screening (POS). Because of the time lag between POS and admission, changes in medication may lead to medication errors at admission (MEA). In a previous study, a risk prediction model for MEA was developed.

Objective

To validate this risk prediction model to identify patients at risk for MEA in a university hospital setting.

Methods

The risk prediction model was derived from a cohort of a Dutch general hospital and validated within a comparable cohort from a Dutch University Medical Centre. MEA were assessed by comparing the POS medication list with the reconciled medication list at hospital admission. This was considered the gold standard. For every patient a risk score using the risk prediction model was calculated and compared with the gold standard. The risk prediction model was assessed with receiver operating characteristic (ROC) analysis.

Results

Of 368 included patients, 167 (45.4%) had at least one MEA. ROC analysis revealed significant differences in the area under the curve of 0.535 ($p=0.26$) (validation cohort) versus 0.752 ($p<0.0001$) (derivation cohort). The sensitivity in this validating cohort was 66% with a specificity of 40%.

Conclusion and Relevance

The risk prediction model developed in a general hospital population is not suitable to identify patients at risk for MEA in a university hospital population. However, number of medications is a common risk factor in both patient populations and should thus form the basis of an adapted risk prediction model.

INTRODUCTION

Medication errors at admission (MEA) occur frequently and have potential clinical relevance.[1,2] To reduce these MEA, medication reconciliation implementation in hospital transitions is recommended by the World Health Organization and the Joint Commission.[3,4] The WHO describes medication reconciliation as "the formal process in which health care professionals' partner with patients to ensure accurate and complete medication information transfer at interfaces of care".[3] Pharmacy-led medication reconciliation, which is considered the most cost-effective intervention[5], can lead to a 66% reduction in medication errors.[6] In the Dutch guideline on prevention of MEA, medication reconciliation is required within 24 hours of admission.[7] In patients who will undergo elective surgery, medication reconciliation is often part of the preoperative screening (POS).[8] However, the time window between the POS and admission is usually larger than 24 hours.[9] Therefore, medication reconciliation should be repeated at admission to comply with the guideline.

To be able to select patients at high risk for MEA, risk factors need to be investigated. Hias et al.[10] showed in a review that number of preadmission drugs and age have a predictive value for discrepancies. They advise to validate these variables in risk prediction models.

In agreement with the results of the above mentioned review, we identified the number of medications in an earlier study in a general hospital as a potential risk factor for discrepancies. In addition, respiratory comorbidity was identified as a potential risk factor for patients with MEA after medication reconciliation at the POS in a multivariate logistic model. Cardiovascular comorbidity was only significant in the univariate analysis.[9] From the data of this study, a risk prediction model was constructed, containing these three variables. Although in this study the time between POS and admission was not identified as a potential risk factor, in 67% of the patients no difference in medication between POS and admission was found. Therefore, if patients at risk can be selected this could prevent a second interview in these patients. The ultimate aim is to use such a risk prediction model to identify patients at risk for MEA in all types of hospital settings, and to perform the second pharmacy-led medication reconciliation at admission in these patients at risk for an MEA only. This would result in a more efficient process, reducing workload for the clinical pharmacy and preventing redundant questions for patients at admission. To our knowledge there are no earlier studies that investigated a risk-prediction model to select patients at high-risk for medication errors.

To validate if the risk prediction model developed in the general hospital patient population can predict medication errors at admission correctly in a university hospital population, we performed this study. The secondary objectives are to identify potential additional risk factors for MEA in a university medical patient population and to evaluate the characteristics of these MEA.

METHODS

Study design

For the derivation cohort we used an observational quantitative study design, in which medication discrepancies were identified by comparing the preoperatively screened medication with the medication at hospital admission.

For the validation cohort the same study design was used to retrieve the gold standard data. In addition, for each patient the outcome of the risk prediction model was calculated and compared to the gold standard.

Derivation cohort

The risk prediction model that was validated in this study was derived from a general hospital setting (Zaans Medical Centre, Zaandam, The Netherlands). The Zaans Medical Centre is a 300 bed general hospital with around 12,500 clinical admissions every year. Patients were included at the POS when given informed consent, were 18 years or older, and admitted to hospital for at least 24 hours. Exclusion criteria were patient or accompanying caregiver was not able to participate in the medication reconciliation, or a patient received additional pre-surgery medication reconciliation by the admitting medical ward. Patients were included between October 26 and December 18, 2015. The primary outcome was the proportion of patients with one or more MEA.[9] Medication reconciliation consisted of a standardized medication interview with the patient performed by a researcher (pharmacist or pharmacist in training). The researcher was trained to work according to the medication reconciliation method used by the pharmacy technicians at the POS. When available, a recently obtained community pharmacy record, a medication list brought by the patient and/or his medication boxes were used to verify actual medication use with the patient. In case the patient could not answer these questions completely, the accompanying caregiver was interviewed as well. Medication reconciliation took place either pre- or post-operatively. Discrepancies between medications at the POS and medications at admission were divided into intentional and unintentional discrepancies using the patient medical record and if necessary information from the attending physician. Discrepancies were seen as intentional if home medication was intentionally altered during admission. Unintentional discrepancies are defined as home medication that was not correct in the electronic record and confirmed by a physician that it was unintentional. Unintentional medication discrepancies between the hospital electronic medical record and the actual used medication were defined as medication errors at admission (MEA). When an MEA was found, this was communicated with and corrected by the attending physician.

Validation cohort

The validation cohort was derived from patients admitted for elective surgery in a university hospital setting and performed at the Leiden University Medical Centre

(LUMC) in The Netherlands. The LUMC is a 800 bed university hospital with around 25,000 clinical admissions every year. The study received a waiver from the Medical Ethics Committee of the LUMC, as it complied with the Medical Research in Humans Act. Patients were included between October 17, 2016 and August 29, 2017. The data was prospectively collected using the same methods as in the derivation cohort.

Outcome

The primary outcome was the proportion of patients with one or more MEA. This outcome was used as the gold standard, to which the outcome predicted by the risk prediction model was compared. Sensitivity and specificity, were reported. The area under the curve (AUC) of the receiving operating characteristics (ROC) curves from the derivation cohort[9] and the validation cohort were compared. Secondary outcomes were potential risk factors for MEA in the validation cohort, type and severity of the MEA as well as the type of medications involved in the MEA.

Candidate predictors

The following patient characteristics were collected in the validation cohort as candidate predictors of MEA: age, sex, time in days between preoperative screening and admission, number of medications at the POS and admission, level of education, presence of comorbidities (cardiovascular disease, hypertension, respiratory disease, cerebrovascular accident, kidney disorder, thrombosis/embolism, diabetes mellitus, thyroid disorder), ward type and medical specialty. In the medication reconciliation interview the number of medications and the level of education (primary school, secondary school, high school, vocational education, university of applied sciences or university) was determined.

Classification of medication errors and medication types

The MEA were classified by error type and severity. Three types of medication errors were defined: omission (not in the hospital record, but observed to be in use), commission (in the hospital record, but not observed to be in use) and frequency/dose (medication in the hospital record, but in another frequency or dose than observed). The severity of the MEA was classified using the NCC MERP medical error index (Figure 1).[11] Category A and B were not included as medication errors in this study, because these are categories that did not reach the patient. Therefore MEA were classified in category C to I. The identified MEA were assessed with respect to NCC MERP severity class by two hospital pharmacists (KG and ME) independently from each other. In case their assessments differed, they met to reach consensus. Anatomic Therapeutic Chemical (ATC) code of medications involved in MEA was noted, to evaluate which medication subclass was more involved in MEA.[12]

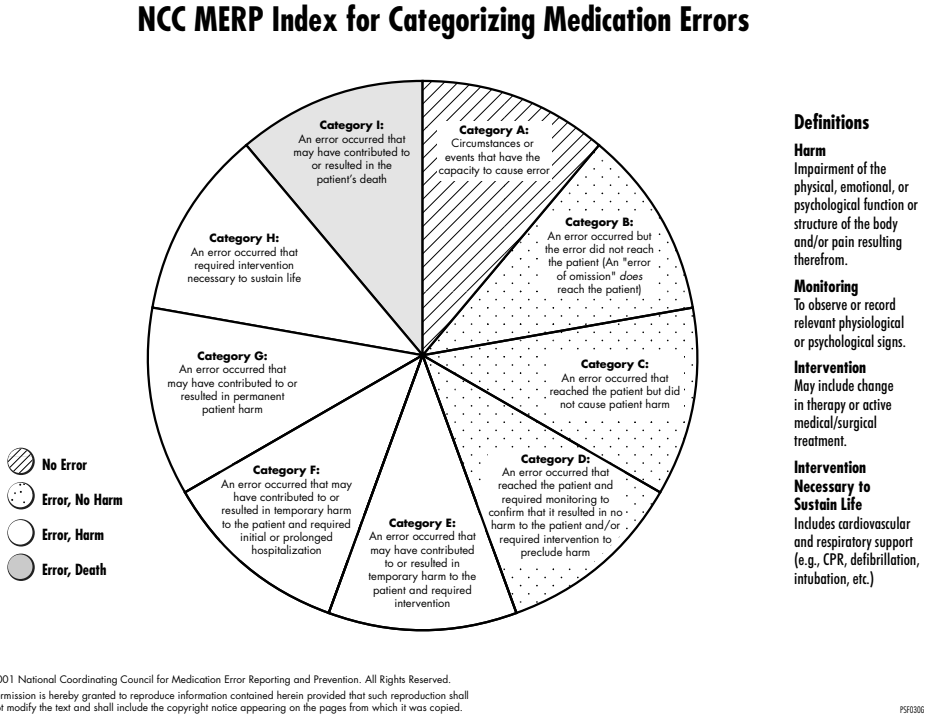

Figure 1. NCC MERP index for categorizing medication errors[11]

Risk prediction model

The risk prediction model, that was developed from the data of the derivation cohort[9], was: Risk score = 0.152 * N + 0.907 * C + 1.446 * R. In which N = number of medications at POS, C = cardiovascular comorbidity, and R = respiratory comorbidity. Other patient characteristics did not remain significant in the multivariate risk prediction model. From the ROC curve of this development cohort the risk score of 0.5 was chosen as cut-off with a sensitivity of 70% and specificity of 62%. For every patient from the validation cohort the risk score was calculated using this risk prediction model. Every patient with a risk score above 0.5 was defined as a patient at risk for MEA.

Model validation

The required sample size for the validation cohort was estimated at 162 patients with an MEA, using the sensitivity of 70%, alpha of 0.025 and beta of 0.20 and a sensitivity of 60% or higher as equivalent proportion. Based on an estimated prevalence of 33%[9], a sample size of 500 patients was calculated. The study protocol included an interim analysis after 300 patients to evaluate the prevalence of MEA and if necessary to adjust the sample size. The data were transferred from OpenClinica version 3.8 (OpenClinica LLC, Waltham, USA) to SPSS Statistics version 23 (IBM Corp, Armonk, NY) for analysis.

The proportion of patients with MEA was calculated dividing the patients with MEA by the total number of included patients. For every patient the actual occurrence of MEA was compared to the predicted occurrence of MEA. The diagnostic value of the prediction model was established by calculating the sensitivity and specificity. The ROC curves of the risk prediction model and these validation parameters were compared to establish the fit of the model.

Secondly, the association of all potential risk factors with the occurrence of MEA was analysed using univariate logistic regression. If the p-value was < 0.20, the parameter was analysed in a stepwise backwards multivariate logistic regression model and was retained in the model if it changed the beta coefficient with more than 10%. Odds ratio's (OR) and 95% confidence intervals (95% CI) were reported. Type and severity of MEA and type of medication was analysed using descriptive statistics.

RESULTS

After screening of 1005 patients, 368 patients were included according to the study flow in Figure 2. The most common cause for exclusion was the availability of patients for the interview (59%). Of these non-available patients 152 (24%) were not included due to transfer to a medical ward where the study was not executed. Another 10% was due to the patient being asleep at the time the researcher arrived and 10% due to other medical staff that was with the patient.

Table 1 shows the general characteristics of the included patients of the validation cohort and derivation cohort. The mean age of the validation population was 61.3 years with a standard deviation (SD) of 13.6 compared to 61.8 with SD 16.3 in the derivation population. Men (52%) and women (48%) were included almost equally in the validation cohort, compared to 42% male and 58% female in the derivation cohort. On average a lag of 27.8 days existed between the POS and admission with a large variation (SD 31.6 days) compared to 32.8 ± 24.8 days in the derivation cohort. On average, patients used 4.7 medications (SD 4.2) at the POS in the validation cohort significantly more than the average of 3.7 medications (SD 3.5) in the derivation cohort. Furthermore the population of the derivation cohort significantly differed in level of education, and occurrence of cardiovascular disease, kidney disorder, and thrombosis/embolism.

Of the 368 patients included, 167 (45.4%) had at least one MEA. For 8 patients the risk score could not be calculated because the cardiovascular comorbidity was unknown. For 360 patients the prediction of MEA using the risk prediction model is compared to the actual occurrence of MEA. This resulted in 108 patients with MEA that were correctly predicted to have MEA and 79 patient without MEA that were correctly predicted to having no MEA. 56 patients had MEA but it was predicted they would not have MEA and 117 patients had no MEA but were predicted to have MEA. The sensitivity in this validating cohort is 66%, with a specificity of 40%. The sensitivity of the derivation cohort is 70% with a specificity of 62%. The ROC curves of the prediction model in the derivation

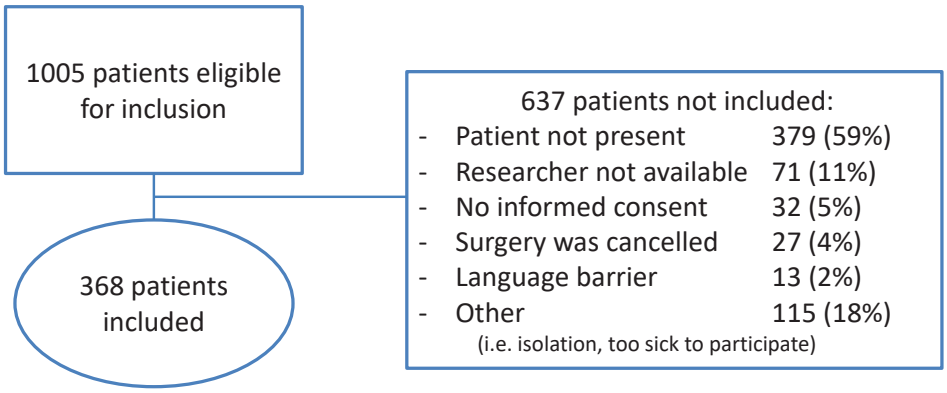

Figure 2. Study flow

Table 1. Patient characteristics for validation cohort (n=368) and derivation cohort (n=183)

	Validation cohort	Derivation cohort	p-value
Age, mean ± SD	61.3 ± 13.6	61.8 ± 16.3	0.704
Sex (female), N (%)	176 (48%)	106 (58%)	0.199
Days between POS and admission, mean ± SD	27.8 ± 31.6	32.8 ± 24.8	0.062
Number of medications at POS, mean ± SD	4.7 ± 4.2	3.7 ± 3.5	0.006*
Number of medications at admission, mean ± SD	4.8 ± 4.0	3.6 ± 3.5	0.001*
Level of education, N (%)			0.029*
Primary school	35 (10%)	14 (8%)	
Secondary school	72 (20%)	43 (23%)	
High school	25 (7%)	9 (5%)	
Vocational education	98 (27%)	72 (39%)	
Univeristy of applied sciences	69 (19%)	35 (19%)	
University	43 (12%)	10 (5%)	
Unknown	26 (7%)	-	
Comorbidities, N (%)			
Cardiovascular disease	75 (21%)	22 (12%)	0.012*
Hypertension	136 (37%)	55 (30%)	0.104
Respiratory disease	45 (12%)	22 (12%)	0.946
Cerebrovascular accident	17 (5%)	10 (5%)	0.835
Kidney disorder	30 (8%)	6 (3%)	0.020*
Thrombosis/embolism	32 (9%)	4 (2%)	0.003*
Diabetes mellitus	46 (13%)	19 (10%)	0.390
Thyroid disorder	27 (7%)	17 (9%)	0.486

Abbreviations: POS = preoperative screening, SD = standard deviation,
*p<0.05

and validation cohort are shown in Figure 3. The AUC of the validation cohort is 0.535 (p = 0.26). This means only half of the MEA is predicted correctly by this model and this is not significantly better than chance. The AUC of the ROC curve of the derivation cohort is 0.752 (p <0.0001). This means about 75% of the MEA are correctly predicted by this model and this is significantly better than chance.

In Table 2 the results of the univariate logistic regression analysis are presented. Only the number of medications at admission OR 1.06 (95% CI 1.01-1.12) was significantly associated with the occurrence of MEA. In the stepwise backwards multivariate logistic regression, the two potential risk factors that showed a p-value below 0.20 in the univariate analysis were analysed. None of the variables remained in the equation and therefore the results of the univariate analysis are the final results for the associated potential risk factors. No additional risk factors were identified.

In the 167 patients with at least one MEA, 302 MEA were found. Of these MEA 145 (48%) were omissions, 90 (30%) were commissions and 67 (22%) consisted of changes in dose/frequency. 193 (63%) of the MEA in 133 (36%) patients, were classified to at least have the potential to be harmful (NCC MERP category D, E or F). Medications of the 'Alimentary tract and metabolism' (26%) ATC class were most frequently involved in MEA, followed by 'Nervous system' (18%), 'Dermatologic' (12%) and 'Respiratory medication' (11%).

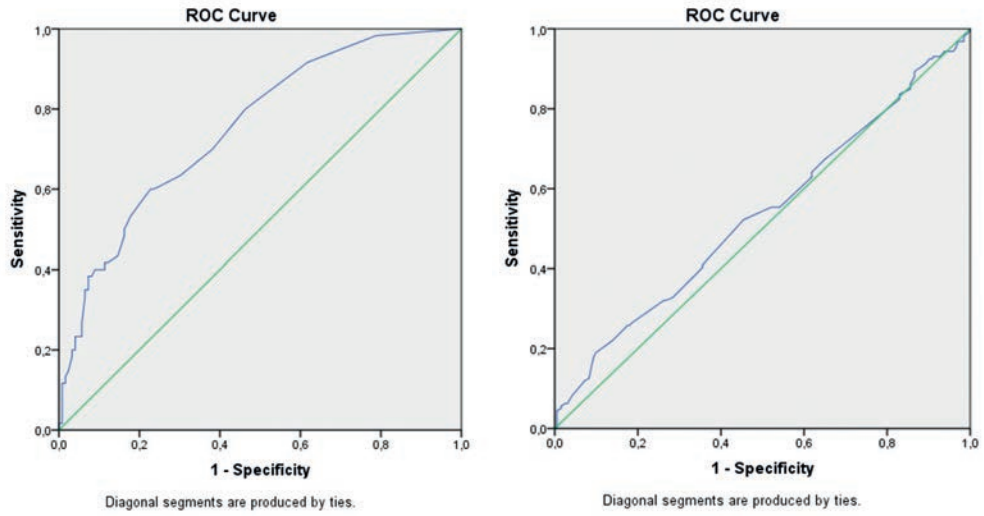

Figure 3. Receiving Operater Characteristic curves of the prediction model in the derivation vs the validation cohort. Receiving Operator Characteristics curves; the curved line is the prediction of a medication error at admission (MEA) vs the real occurrence of MEA. The straight line is the reference. On the left: derivation cohort, the area under the curve (AUC) is 0.752 p-value <.0001. On the right: validation cohort, the AUC is 0.535 p-value 0.26.

Table 2. Univariate logistic regression of patient factors associated with medication errors at admission

Parameter	Odds Ratio (95%-confidence interval)
Age	0.92 (0.98-1.01)
Sex	0.92 (0.61-1.39)
Number of medications at preoperative screening	**1.06 (1.01-1.12)***
Time in days between preoperative screening and admission	**1.00 (0.99-1.01)**
Level of education[a]	
Secondary school	1.59 (0.70-3.60)
High school	2.14 (0.70-6.97)
Vocational education	0.90 (0.18-4.38)
University of applied sciences	1.03 (0.47-2.27)
University	0.91 (0.39-2.09)
Comorbidities	
Cardiovascular disease	**0.94 (0.56-1.56)**
Hypertension	**1.07 (0.70-1.63)**
Respiratory disease	**1.58 (0.84-2.96)****
Cerebrovascular accident (CVA)	**1.37 (0.52-3.64)**
Kidney disorder	**1.23 (0.58-2.61)**
Thrombosis/embolism	**1.59 (0.77-3.31)**
Diabetes mellitus	**0.76 (0.40-1.43)**
Thyroid disorder	**1.33 (0.61-2.92)**

[a]Primary school is the reference level
*p-value < 0.05
**p-value < 0.20

DISCUSSION

This study showed that the risk prediction model developed with data from the derivation cohort[9] is not suitable to predict MEA in patients in the validation cohort. In this study 45.4% of included patients had at least one MEA. This is substantially higher than the results of earlier studies[6,13] and 12% higher than the derivation cohort[9]. This could be explained by the more complex patient population in the university hospital setting from the validation cohort. Cardiovascular comorbidity occurred almost twice as often (21% versus 10%) and kidney disorder and thrombosis occurred more than twice as often in the validation cohort (respectively 8% versus 3%; 9% versus 2%). Furthermore, more patients (36% vs 9%) had a potentially harmful MEA in the validation cohort. This confirms the more complex patient population in the university hospital setting.

The higher percentage can also be explained by the higher number of medications used (average 4.7 compared to 3.7). In the logistic regression number of medications at the POS is significantly associated with the occurrence of MEA. This corresponds with the findings of earlier studies.[8,10]

Compared to the derivation cohort more omissions were found, comparable with earlier studies.[1,13] The ATC medication classes most frequently involved in MEA were the same as in the derivation cohort. The medication classes 'Alimentary tract and metabolism', 'Nervous system', 'Dermatologic', and 'Respiratory medication' should get more attention in the medication reconciliation process. Unfortunately the medication class is not suitable as a risk factor to predict MEA because most MEA are omissions and therefore the medication class is not known at the moment of risk assessment.

This is the first validation study of a risk prediction model for patients at risk for MEA. A strength of this study is that it included patients of all surgical specialties and therefore the findings are representative for daily clinical practice. The number of medications is represented in the risk prediction model and is an independent risk factor associated with MEA in the validation cohort as well, confirming the importance of this potential risk factor. Another strength of this study is that the derivation cohort and validation cohort are studied applying the same study procedures.

Some limitations need to be discussed. First of all more than half of the eligible patients are not included in the validation cohort. This is explained by the fact that patients who undergo surgery are often not in their hospital bed due to the surgery itself but also because of different appointments to help recover after surgery. However, we do not expect this to result in selection bias, as these logistic reasons apply to all patients. In February 2017 the gynaecology department of the LUMC introduced an intervention to perform a second medication reconciliation for every patient in the week before admission. Therefore when this intervention started the gynaecology department was excluded in this study. This means that only during half of the inclusion time of the validation cohort, patients of this specialty could participate in the study. However, we do not believe this affected the results because no difference has been demonstrated between the medical specialties. Another limitation of this study is that differences in medication overview after medication reconciliation can be caused by different approaches of the interview instead of actual changes in medication between the two medication reconciliation moments. Patients could forget to mention a medicine at the POS and remember it again at admission. We tried to minimize this risk by performing both medication reconciliation interviews according to the same protocol. However, we did not ask the patients when medication changes were discovered, where these changes originated from.

Future research is necessary to be able to identify high-risk patients with a better specificity and sensitivity. For the time being it is advised to perform a second medication reconciliation in elective patients at admission because 45% of patients still have MEA. To prevent the unnecessary performance of medication reconciliation in more than half of the patients better prediction models are necessary to select patients at high risk for an MEA. Future research that combines data from different patient populations would be helpful to establish this.

CONCLUSION AND RELEVANCE

The risk prediction model developed in a general hospital patient population is not suitable to identify patients at risk of medication errors at admission (MEA) in a university hospital patient population. This may be due to the more complex patients in the university hospital patient population. The number of medications is a common risk factor in both patient populations and should thus form the basis of an adapted risk prediction model.

REFERENCES

1. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ, 2005;173(5):510-515. DOI: 10.1503/cmaj.045311
2. Quellenec B, Beretz L, Paya D, et al. Potential clinical impact of medication discrepancies at hospital admission. Eur J Intern Med, 2013;24:530-535. DOI: 10.1016/j.ejim.2013.02.007
3. World Health Organization. Assuring Medication Accuracy at Transitions in Care: Medication Reconciliation. http://www.who.int/patientsafety/implementation/solutions/high5s/h5s-sop.pdf Updated, September 2014. Accessed, April 2018.
4. Joint Commission Sentinel Event Alert – Using medication reconciliation to prevent errors. Issue 35; Jan 25, 2006
5. Karnon J, Campbell F, Czoski-Murray C. Model-based cost-effectiveness analysis of interventions aimed at preventing medication error at hospital admission (medication reconciliation). J Eval Clin Pract, 2009;15(2):299-306. DOI: 10.1111/j.1365-2753.2008.01000.x
6. Mekonnen AB, McLachlan AJ, Brien JA. Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis. J Clin Pharm Ther, 2016;41(2):128-144. DOI: 10.1111/jcpt.12364
7. Dutch Federatie Medisch Specialisten and Ministry of Health Welfare and Sports. Leidraad Overdracht van Medicatiegegevens in de keten. http://www.nhg.org/. Updated November 2017. Accessed December 30, 2017
8. van den Bemt PM, van den Broek S, van Nunen AK, Harbers JB, Lenderink AW, Medication reconciliation performed by pharmacy technicians at the time of preoperative screening. Ann Pharmacother, 2009;43(5):868-74. DOI: 10.1345/aph.1L579
9. Ebbens MM, Gombert-Handoko KB, Al-Dulaimy M, van den Bemt PMLA, Wesselink EJ. Risk factors for medication errors at admission in preoperatively screened patients. Pharmacoepidemiol Drug Saf. 2018 Mar;27(3):272-278. DOI: 10.1002/pds.4380
10. Hias J, van der Linden L, Spriet I, et al. Predictors for unintentional medication reconciliation discrepancies in preadmission medication: a systematic review. Eur J Clin Pharmacol, 2017;73(11):1355-1377. DOI: 10.1007/s00228-017-2308-1
11. National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP). Types of Medication Errors. 1996. http://www.nccmerp.org/types-medication-errors. Updated 2001. Accessed April 2018.
12. WHO Collaborating Centre for Drug Statistics Methodology. Complete ATC index 2016. http://www.whocc.no/atcddd/. Updated December 20, 2017 Accessed December 30, 2017.
13. Kwan Y, Fernandes OA, Nagge JJ, et al., Pharmacist medication assessments in a surgical preadmission clinic. Arch Intern. Med, 2007;167(10):1034-1040. DOI: 10.1001/archinte.167.10.1034

PART II

PERFORMING MEDICATION RECONCILIATION IN A MORE EFFICIENT WAY

CHAPTER

6

MEDICATION RECONCILIATION AT THE PREOPERATIVE SCREENING BY PHARMACY TECHNICIANS COMPARED TO ANAESTHESIOLOGISTS

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ABSTRACT

Background and aims

Medication reconciliation by pharmacy personnel is a safety intervention aimed at reducing the risk of medication errors at transitions of care. The number of medications per patient is a well-established risk factor of these errors. Therefore, stratification of the performer of medication reconciliation (physician during routine activities or pharmacy technician) by the number of medications may be an efficient approach. To evaluate the safety of this method we performed this study.

Methods

An observational prospective study was performed in elective surgery patients in the Leiden University Medical Center (LUMC), the Netherlands. The study was approved by the Medical Ethics Committee of the LUMC. Medication reconciliation was performed at preoperative screening (POS) by pharmacy technicians when patients used >1 medication, while anaesthesiologists performed medication reconciliation in all other patients . Medication reconciliation was repeated at admission by a researcher. Patients admitted for at least 24 hours, who were ≥18 years, and were able to participate in a medication reconciliation interview were included between October 2016 and August 2017. The primary outcome was the proportion of patients with one or more medication errors at admission (MEA).This was corrected for differences in patient characteristics using multivariate logistic regression.

Results

Of 367 patients, medication was reconciled by the pharmacy technician in 201 patients and in 166 patients by the anaesthesiologist. The percentage of patients with at least one MEA was 47% and 44% respectively, in multivariable analysis adjusted for number of medication, age, days between POS and admission, cardiovascular disease, hypertension, diabetes and cerebrovascular accident OR_{adj} 1.66 (0.99-2.80).

Conclusion

The percentage of patients with at least one MEA did not differ between anaesthesiologists and pharmacy technicians. Therefore we conclude that allocating patients to an anaesthesiologist to perform medication reconciliation when using one or no medication is safe.

INTRODUCTION

Medication errors during hospitalization occur in up to 67% of patients.[1] More than half of these medication errors could have been prevented.[2] Medication errors can lead to adverse drug events and can cause serious morbidity and mortality, as well as a rise in healthcare costs.[3] Performing medication reconciliation may lead to a reduction of medication errors. This approach identifies medication errors in up to 98.2% of patients during hospital admission and discharge.[2-5] Medication reconciliation at the moment of hospital admission generally consists of an interview with the patient, combined with a medication overview from the community pharmacy to obtain the best possible medication history (BPMH).[6] For elective surgery patients the medication reconciliation can be incorporated into the preoperative screening (POS). The advantage of the medication reconciliation at this stage is that the BPMH can be used by the anaesthesiologist in the screening process, to give instructions to patients on which medications to stop or continue in relation to surgical procedures.

Several studies have shown that medication errors are reduced to a greater extent when the interview with the patient is conducted by hospital pharmacists and pharmacy technicians rather than conducted by physicians and nurses.[2,7] But performing medication reconciliation by a pharmacy professional for every patient is a time-consuming safety intervention, which adds costs when compared to implementation of medication reconciliation into routine physician activities. Therefore a risk driven approach is often chosen as is advised by the latest Dutch guideline on medication reconciliation[9].

As the number of medications is associated with the risk of medication transfer errors[10–13], pharmacy technicians should perform medication reconciliation for patients using a higher number of medications. It may be more efficient to have another healthcare professional such as an anaesthesiologist perform medication reconciliation for patients who use little or no medications. In this study anaesthesiologists perform medication reconciliation at the preoperative screening in patients who use one or no medication and pharmacy technicians in all other patients. Whether this strategy is safe is yet unknown. Therefore, the aim of this study was to compare the proportion of patients with one or more medication errors as well as the severity of the medication errors at admission between anaesthesiologists and pharmacy technicians

METHODS

Study design

A prospective observational cohort study was performed in patients admitted for elective surgery in the Leiden University Medical Center (LUMC) in The Netherlands. Ethical approval for this study (Ethical Committee N° P16-180) was provided by the Ethical Committee 'CME' of Leiden University Medical Centre, Leiden, The Netherlands (Chairperson Prof. dr. A. Dahan) on 11 October 2016. Inclusion started October 17th 2016. The last patient was included on August 29th 2017. Data of this study were collected

to study risk factors for medication errors in all patients[14], and are currently used to investigate the differences between pharmacy technicians and anaesthesiologists.

Study population

Patients were included if they were at least 18 years, received elective surgery for which a POS was conducted, and gave informed consent to use data from their electronic medical records. Patients were excluded if they were not able to participate in the medication reconciliation and did not have an accompanying caregiver who could, or were discharged within 24 hours of admission. Finally, one ward introduced additional pre-surgery medication reconciliation by telephone in the study period, and from that moment patients from that ward were excluded to prevent recall bias.

According to standard procedures for medication reconciliation during POS at the LUMC, patients using more than one medication were seen by the pharmacy technician for medication reconciliation at the POS. After the medication reconciliation by the pharmacy technician the patient would visit the anaesthesiologist for pre-operative screening. For all other patients, medication reconciliation was performed by the anaesthesiologist as part of the POS. Since the usual time lag between POS and admission, medication reconciliation was repeated at admission, to comply with the Dutch guideline on medication reconciliation[9], which requires medication reconciliation to be performed within 24 hours of admission. In daily routine the admitting physician would ask if medication had changed between POS and admission.

The second medication reconciliation took place within 48 hours of admission. The period of 48 hours was chosen to be able to include patients the day after surgery. Normally hospital admission took place just before surgery, therefore the day after surgery was also included in this research. At admission, the medication reconciliation interview with the patient was performed by a researcher, who was trained to work according to the medication reconciliation method used by the pharmacy technicians at the POS.

Data collection

The following patient characteristics were recorded from the electronic patient record: number of medications at the POS and the healthcare provider (anaesthesiologist or pharmacy technician) who conducted the reconciliation at the POS. In the medication reconciliation interview at admission the number of medications was determined, as well as the type of medication according to the Anatomic Therapeutic Chemical (ATC) code.[15]

The medications of the medication reconciliation at admission were compared to the medications in the electronic patient record. Furthermore, the electronic patient record was used to assess whether medication differences were intentional or unintentional. If necessary for this assessment, the attending physician was contacted for additional information.

Classification of medication errors

Differences between medications registered in the patient medical record and medications used by patients at admission (the second medication reconciliation) were divided into intentional and unintentional discrepancies. Unintentional discrepancies were defined as medication differences without communication of the attending physician that the medication was deliberately changed. These unintentional discrepancies were then registered as medication errors at admission (MEA). When an MEA was found, this was communicated to the attending physician to prevent unwanted harm to the patient. Subsequently, the MEA were classified by error type and severity. Three types of medication errors were defined: omission (not in the reconciled medication in the electronic patient record, but assessed as being in use at admission), commission (in the reconciled medication in the electronic patient record, but assessed as not being in use at admission) and frequency/dose difference (medication in the reconciled medication in the electronic patient record, but in another frequency or dose than assessed at admission). The severity of the MEA was classified independently by two hospital pharmacists (KG and ME) using the NCC MERP medical error index (Table 1).[16] In case their assessments differed, they met to reach consensus.

Outcome measures

The primary outcome was the proportion of patients with at least one MEA. The outcome in patients seen by the anaesthesiologist was compared to patients seen by the pharmacy technician to evaluate if there was a difference between the two groups. Secondary outcomes were the type and severity of the MEA. In addition, the fidelity of the intervention was checked by establishing the number of medications actually in use by the patient. The fidelity was assessed as either according to protocol (patient seen by

Table 1. NCC MERP medical error severity categories.[16]

Category	Definition
A	No error occurred but circumstances or events had the capacity to cause error
B	An error occurred, but the medication did not reach the patient.
C	An error occurred that reached the patient, but did not cause the patient harm.
D	An error occurred that resulted in the need for increased patient monitoring, but not patient harm
E	An error occurred that resulted in the need for treatment or intervention and caused temporary patient harm.
F	An error occurred that resulted in initial or prolonged hospitalization and caused temporary patient harm.
G	An error occurred that resulted in permanent patient harm.
H	An error occurred that resulted in a near-death event
I	An error occurred that caused death

anaesthesiologist and used 0 or 1 medication or seen by pharmacy technician when using 2 or more medications), or not according to protocol (patient seen by anaesthesiologist but using 2 or more medications or seen by pharmacy technician when using 0 or 1 medication). A per protocol analysis was performed, in order to compare the primary outcome between anaesthesiologist and pharmacy technician group for the patients whom medication was reconciled by the correct professional according to protocol.

Data monitoring

Patient data were entered into OpenClinica version 3.8 (OpenClinica LLC, Waltham, MA, USA). OpenClinica is an application with a digital Clinical Registration Form (CRF) in which every action is logged. After data entry, 10% of the data was checked for errors by a second researcher. If an error was discovered another 10% of the data was checked for errors, this was repeated until no errors were discovered or all data were checked. During data analysis data were also checked for missing values and non-existing values. If missing or non-existing values were discovered, data were checked on the original CRF, or electronic patient record and were corrected in the database. After data check the database was locked for analysis.

Data analysis

Data analysis was performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington) and IBM SPSS Statistics version 23 (IBM Corp, Armonk, New York). The proportion of patients with at least one MEA was calculated by dividing the number of patients with one or more MEA by the total number of patients included. Descriptive statistics were used to report type and severity of MEA. Univariate logistic regression was performed on the difference between two groups for the primary outcome. The primary outcome was adjusted for patient characteristics that differed significantly between the two group, by performing forced entry multivariate logistic regression. Results are reported as (adjusted) odds ratios (OR) and 95% confidence intervals (95% CI).

RESULTS

Of 1020 patients screened, 367 patients were included in the study. The pharmacy technician performed medication reconciliation in 201 (54.8%) patients and the anaesthesiologist in 166 (45.2%) patients (Figure 1).

Patient characteristics are shown in Table 2. As patients were allocated by the number of medications they used, patients seen by the pharmacy technician used significantly more medication than patients seen by the anaesthesiologist. Patients in the pharmacy technician group are older and have significantly more comorbidities such as hypertension, cardiovascular disease, cerebrovascular accidents and diabetes.

Of the included patients, 167 (45.5%) had at least one MEA, of which 89/201 (44%) were seen by the pharmacy technician and 78/166 (47%) by the anaesthesiologist

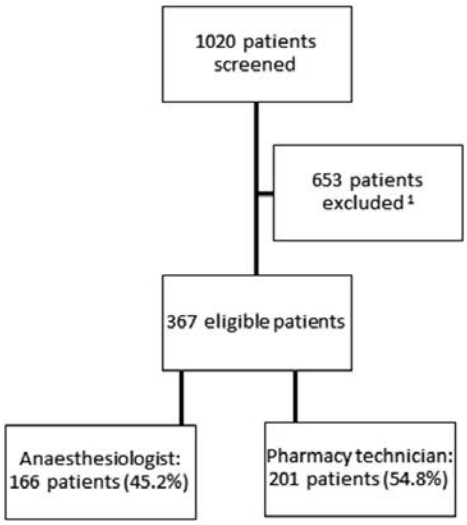

Figure 1. Study flow.[1] Contacting the patient within 48 hours was not always possible, for example due to the following reasons: Patients were not in their room; had visitors or were asleep.

Table 2. Patient characteristics

	Pharmacy technician n = 201	Anaesthesiologist n = 166
Age, mean ± SD	65 ± 11.5	57 ± 14.8
Sex (female), N (%)	102 (51%)	73 (44%)
Days between POS and admission, mean ± SD	29 ± 26	24 ± 25
Number of medications at POS, mean ± SD	6.6 ± 3.7	2.5 ± 3.7
Number of medications at admission, mean ± SD	6.5 ± 3.4	2.8 ± 3.8
Comorbidities, N (%)		
Cardiovascular disease	54 (27%)	20 (12%)
Hypertension	104 (52%)	32 (20%)
Respiratory disease	25 (12%)	20 (12%)
Cerebrovascular accident	14 (7.0%)	3 (1.8%)
Kidney disorder	21 (10%)	9 (5.4%)
Thrombosis/embolism	21 (10%)	11 (6.6%)
Diabetes mellitus	35 (17%)	10 (6.0%)
Thyroid disorder	17 (8.5%)	10 (6.0%)

(Table 2). Results of the univariate logistic regression and multivariate logistic regression are shown in Table 3. No significant differences are shown between anaesthesiologists and pharmacy technicians.

Of 166 patients reconciled by the anaesthesiologist 68 (41.0%) should have been reconciled by the pharmacy technician, since these patients used two or more

Table 3. Frequency of medication errors at admission (MEA).

	Total	Anaesthesiologist (n=166)	Pharmacy technician (n=201)	Statistics
Number of medication errors at admission (MEA) (mean ± SD)	0.87 ± 1.3	0.82 ± 1.2	0.93 ± 1.4	p =0.45[a]
Patients with at least one MEA	167	78 (47%)	89 (44%)	OR 1.12 (95%-CI 0.74-1.69)[b]
Patients with at least one MEA per protocol[c] (n=295)	123 (42%)	37 (38%)	86 (44%)	OR 0.78 (0.48-1.29)[b]
Patients with at least one MEA multivariate analysis	167	78 (47%)	89 (44%)	OR 1.66 (0.99-2.80)[d]
Patient with at least one MEA multivariate per protocol analysis[c]	123	37 (38%)	86 (44%)	OR 1.07 (0.49-2.32)[d]

[a] Result of an unpaired T-test
[b] Result of univariate logistic regression
[c] In the per protocol analysis the 72 patients who were not seen according to protocol were excluded.
[d] Result of a multivariate logistic regression adjusted for number of medications, age, days between POS and admission, cardiovascular disease, hypertension, diabetes and cerebrovascular accident.

medications at the moment of preoperative screening. In the pharmacy technician group, four patients (2.2%) were not seen according to protocol because these patients used one or no medication. Overall, these results indicate that in daily practice the protocol is not adhered to in almost 20% of patients. The results of the per protocol analysis were not different from the intention to treat analysis.

Characteristics of MEA

A total of 293 MEA were found. The most frequent types of errors were omissions, followed by commissions and dose or frequency differences (respectively 49.1%, 29.5% and 21.3%) (Figure 2). These proportions were comparable between the anaesthesiologist and pharmacy technician, although more omissions occurred in patients seen by anaesthesiologist and more frequency or dose changes in patients seen by the pharmacy technician.

The most common category from the medical error severity index involved in MEA was category D, followed by C, E and F (Table 4).

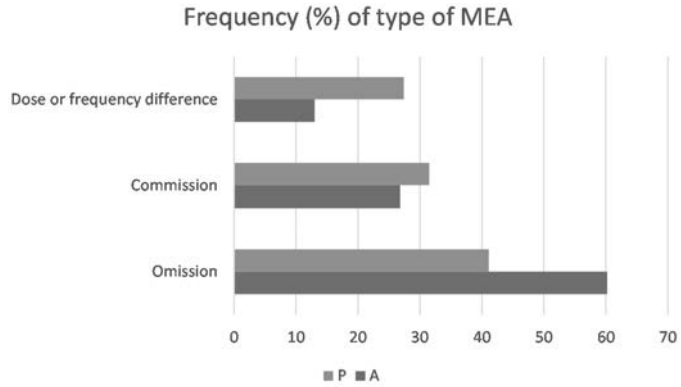

Figure 2. Frequency (%) of types of medication errors at admission (MEA). P = pharmacy technician, A= anaesthesiologist: omission (not in the hospital record, but assessed to be in use), commission (in the hospital record, but not assessed to be in use) and frequency/dose difference (medication in the hospital record, but in another frequency or dose than assessed).

Table 4. NCC MERP category of medication errors at admission for anaesthesiologists and pharmacy technicians.

NCC MERP category	C	D	E	F	Total
Anaesthesiologist n, %	41 (32.8%)	48 (38.4%)	36 (28.8%)	0	125
Pharmacy technician n, %	64 (38.1%)	71 (42.3%)	31 (18.5%)	2 (1.2%)	168
Total n, %	105 (35.8%)	119 (40.6%)	67 (22.9%)	2 (0.7%)	293

DISCUSSION

This study was designed to compare the proportion of patients with at least one MEA between medication reconciliation by the anaesthesiologist and by the pharmacy technician. These proportions were 47% and 44% respectively, a non-significant difference.

This study has shown that in daily practice the protocol is not always followed; almost twenty percent of the included patients were not treated according to protocol. In the per protocol analysis it is shown that if protocol is followed there is no difference between anaesthesiologists and pharmacy technicians.

The most common types of MEA in this study were omissions, which was also shown by Tam et al.[1] Also, most of the MEA fell into the medical error severity classes C and D. This means that most medication errors did not cause any harm to patients.[16] A systematic review conducted by Mekonnen et al. showed that most medication errors did not cause any harm to the patient. Most of these errors belonged to category C.[17] The same was found in a study conducted by Buckely et al.[18] The potential harm of the MEA did not differ between the anaesthesiologist and pharmacy technician.

This study has several limitations. In some cases, the anaesthesiologist conducted the medication reconciliation via a phonecall because the patient could not visit

the hospital. These patients often used more than one drug, thus, normal procedure was not always followed. Second, this study was conducted in a single hospital in a relatively small group, which limits the generalizability and may have reduced the power.

When MEA were corrected for patient characteristics a trend to more MEA was present after medication reconciliation by the anaesthesiologist. With a larger study population this could become a significant result, which would be according to findings in literature where pharmacy professionals reduce medication errors more effectively than physicians and nurses.[2,7]

This may be explained by the fact that pharmacy technicians who perform medication reconciliation solely focus on reconciling the medication. In contrast to anaesthesiologists at the preoperative screening for whom medication reconciliation is one of the many tasks during the outpatient visit.

Also, when patients brought their own medication to the hospital at admission, the physician sometimes deliberately did not record it into the patient medical record. As these patients managed their own medication, for example inhalation medication, dermal preparations or eye drops the physician considered it not necessary to register. This would have resulted in a medication difference between the electronic patient record and the reconciled medication at admission and therefore MEA found in this study could be an overestimation. Nevertheless, the percentages did not differ from existing literature.[7,17] Finally, the classification of medication errors according to NCC MERP medical error severity index relies on subjective judgment and is therefore subject to bias. However, by using two assessors and reaching consensus we have tried to reduce this bias. Nevertheless, this assessment can never replace measurement of actual harm caused by MEA.

This study also has various strengths. It is the first study to evaluate the medication reconciliation performed by two different healthcare professionals stratified by number of medications. Furthermore, we explicitly included only unintentional discrepancies as medication errors. Another strength is that the consensus method was used to assess severity of the medication errors.

However, given the limitations of this study, additional studies are needed to identify the clinical consequences of medication reconciliation errors. Future research should include larger patient populations from different hospitals.

CONCLUSION

After medication reconciliation at the preoperative screening, medication errors at admission still occur. In this study no difference in medication errors at admission was found when reconciliation is performed by a pharmacy technician compared to the anaesthesiologist. Therefore we conclude that allocating medication reconciliation of patients using one or no medication to an anaesthesiologist instead of a pharmacy technician is safe.

REFERENCES

1. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ, 2005;**173(5)**:510-515.
2. Mekonnen AB, McLachlan AJ, Brien JA. Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis. J Clin Pharm Ther 2016 Apr;**41(2)**:128-144.
3. Al-Hashar A, Al-Zakwani I, Eriksson T, Sarakbi A, Al-Zadjali B, Al Mubaihsi S, et al. Impact of medication reconciliation and review and counselling, on adverse drug events and healthcare resource use. Int J Clin Pharm. 2018 Oct;**40(5)**:1154-1164.
4. Lehnbom EC, Stewart MJ, Manias E, Westbrook JI. Impact of medication reconciliation and review on clinical outcomes. Ann Pharmacother. 2014;48(10):1298-1312.
5. Cornu P, Steurbaut S, Leysen T, De Baere E, Ligneel C, Mets T, et al. Effect of medication reconciliation at hospital admission on medication discrepancies during hospitalization and at discharge for geriatric patients. Ann Pharmacother. 2012;46(4):484-494.
6. Institute for Healthcare Improvement (IHI). Medication Reconciliation to Prevent Adverse Drug Events.
7. Mergenhagen KA, Blum SS, Kugler A et al. Pharmacist- versus physician-initiated admission medication reconciliation: impact on adverse drug events. Am J Geriatr Pharmacother 2012; **10(4)**:242-50.
8. Mueller SK, Sponsler KC, Kripalani S, Schnipper JL. Hospital-based medication reconciliation practices: a systematic review. Arch Intern Med. 2012;172(14):1057-1069.
9. Dutch Federatie Medisch Specialisten and Ministry of Health Welfare and Sports. Leidraad Overdracht van Medicatiegegevens in de keten.
10. Hias J, van der Linden L, Spriet I, et al. Predictors for unintentional medication reconciliation discrepancies in preadmission medication: a systematic review. Eur J Clin Pharmacol. 2017;73:1355-1377. doi:10.1007/s00228-017-2308-1
11. Belda-Rustarazo S, Cantero-Hinojosa J, Salmeron-García A, González-García L, Cabeza-Barrera J, Galvez J. Medication reconciliation at admission and discharge: an analysis of prevalence and associated risk factors. Int J Clin Pract 2015;**69(11)**:1268-74.
12. Rodríguez Vargas B, Delgado Silveira E, Iglesias Peinado I, Bermejo Vicedo T. Prevalence and risk factors for medication reconciliation errors during hospital admission in elderly patients. Int J Clin Pharm 2016;**38(5)**:1164-71.
13. González-García L, Salmerón-García A, García-Lirola M, Moya-Roldán S, Belda-Rustarazo S, Cabeza-Barrera J. Medication reconciliation at admission to surgical departments. J Eval Clin Pract 2016;**22(1)**:20-25.
14. Ebbens MM, Laar SAV, Wesselink EJ, Gombert-Handoko KB, van den Bemt PMLA. Prospective Validation of a Risk Prediction Model to Identify High-Risk Patients for Medication Errors at Hospital Admission. Ann Pharmacother. 2018 Dec;**52(12)**:1211-1217. doi: 10.1177/1060028018784905.
15. WHO Collaborating Centre for Drug Statistics Methodology. Complete ATC index 2016. http://www.whocc.no/atcddd/. Updated December 13, 2018 Accessed 23 September 2019.

16. National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP). Types of medication errors. http://www.nccmerp.org/types-medication-errors. Accessed 23 September 2019.

17. Mekonnen AB, Abebe TB, McLachlan AJ, Brien JA. Impact of electronic medication reconciliation interventions on medication discrepancies at hospital transitions: a systematic review and meta-analysis. BMC Med Inform Decis Mak 2016;**16**:112

18. Buckley MS, Harinstein LM, Clark KB et al. Impact of a clinical pharmacy admission medication reconciliation program on medication errors in "high-risk" patients. Ann Pharmacother 2013; **47(12)**:1599-610.

19. Lombardi NF, Mendes AE, Lucchetta RC, Reis WC, Fávero ML, Correr CJ. Analysis of the discrepancies identified during medication reconciliation on patient admission in cardiology units: a descriptive study. Rev Lat Am Enfermagem 2016; **15(24)**:e2760.

20. Gleason KM, McDaniel MR, Feinglass J et al. Results of the Medications at Transitions and Clinical Handoffs (MATCH) study: an analysis of medication reconciliation errors and risk factors at hospital admission. J Gen Intern Med 2010;**25(5)**:441-7.

21. Allende Bandrés MÁ, Arenere Mendoza M, Gutiérrez Nicolás F, Calleja Hernández MÁ, Ruiz La Iglesia F. Pharmacist-led medication reconciliation to reduce discrepancies in transitions of care in Spain. Int J Clin Pharm 2013;**35(6)**:1083-90.

22. Quélennec B, Beretz L, Paya D et al. Potential clinical impact of medication discrepancies at hospital admission. Eur J Intern Med 2013;**24(6)**:530-5.

23. Dufay E, Morice S, Dony A et al. The clinical impact of medication reconciliation on admission to a French hospital: a prospective observational study. Eur J Hosp Pharm 2016;**23**:207-212.

CHAPTER

7

PREVALENCE OF MEDICATION TRANSFER ERRORS IN NEPHROLOGY PATIENTS AND POTENTIAL RISK FACTORS

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ABSTRACT

Background

Medication reconciliation in transitions of care can prevent medication transfer errors (MTE). MTE can cause patient harm. Since performing medication reconciliation for every patient is not always feasible, identification of potential risk factors of MTE could aid in targeting this intervention to the right patients.

Objective

To establish the proportion of patients with one or more MTE in the outpatient nephrology setting. Secondary patient characteristics associated with MTE, type and potential harm, and medication groups were investigated.

Methods

This retrospective observational cohort study was conducted in the Leiden University Medical Center, the Netherlands, between November 2017 and April 2018. The cohort involved patients in whom medication reconciliation was performed by a medical attendant using the electronic tool 'Medical Dashboard' prior to visiting the nephrologist. MTE were defined as unintended discrepancies between the medication in the hospital system and the result of the medication reconciliation. The proportion of patients with one or more MTE was calculated and the association of patient characteristics (age, sex, number of medications and kidney function (CKD-EPI)) with MTE was analyzed using multivariate logistic regression.

Results

Of 380 patients, 235 patients (61.8%) had at least one MTE. On average patients used 10.3 medications. The number of medications per patient was significantly associated with MTE; OR 1.11 (95%CI 1.05-1.16). No association was found for age, sex, and kidney function.

Conclusion

In ambulatory nephrology patients 61.8% had at least one MTE. Nephrology patients using a higher number of drugs are more prone to MTE.

INTRODUCTION

Incomplete medication overviews may increase the risk of patient harm both in and outside the hospital. Approximately two thirds of all patients have at least one discrepancy in their medication overview at hospital admission compared to their home medication.[1,2] Medication reconciliation in transitions of care is known to prevent medication errors.[3,4] The Dutch guideline 'Medication accuracy at transition in care' states that an accurate medication overview is required at each transition point of care.[5] In daily practice medication reconciliation for outpatient visits is not yet implemented in every hospital in the Netherlands, since this is very time consuming. Van der Gaag et al[6] showed that medication reconciliation in an outpatient internal medicine clinic decreased unintentional discrepancies between medication use and the medication reported in the hospital record. Wilson et al[7] provided evidence that ambulatory medication reconciliation increased patient safety and potentially prevented adverse events. In addition, implementation of ambulatory medication reconciliation resulted in improved safety by resolving medication discrepancies in advanced chronic kidney disease patients.[8] Nephrology patients are of special interest, since they often have polypharmacy and medication is frequently adjusted.

Although different studies have shown that medication reconciliation in ambulatory nephrology patients can increase patient safety[6-8], medication reconciliation is a time consuming process. It would be more efficient if this process could be focused on patients at risk of medication transfer errors. This would require knowledge of potential risk factors. A number of studies have been performed with the aim to determine risk factors of medication errors at admission. The most prevalent risk factors are higher age and number of medications.[4,9] A review of Hias et al.[2] has identified sixteen significant variables, of which higher age and polypharmacy were the most frequently found risk factors for medication errors at admission. In ambulatory primary care patients the number of medications in use was significantly associated with the occurrence of medication discrepancies.[10] However, nephrology patients use, on average, much more medication than the average primary care patient. Furthermore, nephrology patients usually have other comorbidities and visit different health care professionals.[7,8] Due to many different health care providers more Medication transfer errors (MTE) could occur, because at each contact medication reconciliation may fail. On the other hand, because nephrology patients are used to taking a lot of medications they could be more involved in their medication use and therefore less MTE could occur. Furthermore in nephrology patients the stage of the kidney disease varies over time and therefore a lot of medication adjustments are frequently necessary.

Due to these reasons, the risk factors found in primary care might not be applicable to the nephrology outpatient population. To our knowledge, in ambulatory nephrology patients no studies have been performed to identify risk factors of medication errors. A few studies have been performed to determine the prevalence of MTE in nephrology outpatients, however the percentage of errors differs between 48 and 80%. [6-8] Therefore,

the primary aim of this study was to establish the proportion of patients with one or more medication transfer errors. The secondary aim was to identify characteristics associated with medication transfer errors in the outpatient nephrology setting, as well as to study the type and potential harm of the medication transfer errors and the medication groups involved.

METHODS

Study design

This retrospective observational cohort study was conducted in the Leiden University Medical Center (LUMC), the Netherlands. According to the Dutch Medical Research in Humans Act, medical ethical approval was not required and patients did not need to provide informed consent, since their data were handled anonymously by the researcher. All patient data were coded according to Dutch Privacy Law. Only the treating physician had access to the code key and thus the patient data.

Study population

All patients using medication visiting the outpatient transplant nephrology clinic between November 13th 2017 and April 24th 2018, were included in the study. If a patient visited the nephrologist multiple times during the research period only the first visit was included.

Data collection

Medication reconciliation was performed by a medical attendant who is familiar with the medication of these nephrology patients and received specific training to use the tool 'Medical Dashboard' to perform medication reconciliation. The 'Medical Dashboard' combines information about medication use from the electronic patient record of the hospital with medication dispensing information from the community pharmacy obtained through the 'Landelijk Schakelpunt' (LSP). The medication is than shown in the Medical Dashboard grouped by medication class. Doublings between LSP and the electronic patient record are therefore comprehensively shown in lines below each other. The medication overview of the electronic hospital patient record is a combination of outpatient and inpatient medication prescribed at the hospital. The LSP is an electronic connection tool from which drug dispensing information of the community pharmacy can be obtained by a health care provider, if the patient has given consent to the community pharmacy (or several community pharmacies, should they visit more than one). The generated medication list in the 'Medical Dashboard' was discussed with the patient during an interview with the medical attendant. For each drug on the list the medical attendant could select one of the following options: correct, adjust, remove, 'add from LSP', or 'patient does not know'. If the medical attendant did not select any of these options it was scored as unknown. After screening the known medication from the two sources, medication that was in use but not available in one of the two sources could be added. The following patient characteristics were derived from the hospital electronic

patient record: age, gender, number of prescription medications at the outpatient visit and kidney function (most recent glomerular filtration rate, as calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)) .

Medication transfer errors

Medication discrepancies were defined as any difference in medications, dose, frequency or route between the medication in the hospital electronic patient record and the result of the medication reconciliation recorded in the 'Medical Dashboard'. All identified medication discrepancies were considered unintended, because medication reconciliation took place before the medical specialist could prescribe any new medication that could be considered as an intended discrepancy. For this reason, the medication discrepancies were defined as medication transfer errors (MTE). The MTE were classified into three categories: omission (observed to be in use but not recorded in the electronic patient record); commission (not observed to be in use, but documented in the electronic patient record) and change in dose, frequency, or route. Potential harm of the MTE was assessed using the National Coordinating Council on Medical Reporting and Prevention (NCC-MERP) classification system.[11] Categories A and B of the NCC-MERP were not included in this study because these are categories that do not reach the patient. Therefore, MTE were classified in category C to I. (Table 1) Two authors (ME and HE) scored individually. When there was no agreement a third author (KG) was consulted to make the final decision.

Outcome

The primary outcome was the proportion of patients with one or more medication transfer errors (MTE). The secondary outcome was the association of potential risk factors with these MTE and the type and potential harm of the MTE, and the medication groups involved in the MTE were investigated.

Data analysis

The sample size calculation was based on the incidence of medication transfer errors in the intervention group of Van der Gaag et al[6] of 38%, an alpha of 0.05 and the assumption that not more than four independent variables (age, gender, number of medications and kidney function) would be included. Using these data a minimum of 105 patients was required.

The dataset was extracted from usual care data. To validate these data unusual values and duplicates were checked. Since different ways to record a change in dose in the 'Medical Dashboard' system were possible, all dose changes were checked and recoded.

Data were collected in Microsoft Excel 2010 (Microsoft Cooperation, Redmond, Washington, USA). Data analysis was performed in IBM SPSS Statistics version 24 (IBM Corporation, Armonk, New York, USA). Using descriptive statistics, mean and standard deviations or total number and percentages were reported.

Table 1. Potential harm of the medication transfer errors

Category	Occurrence (%)	Definition	Example
A	0	Circumstances or events that have the capacity to cause error	NA[a]
B	0	An error occurred but the error did not reach the patient (An "error of omission" does reach the patient)	NA[a]
C	172 (29%)	An error occurred that reached the patient but did not cause patient harm	*Example:* Frequency change of alfacalcidol 0.25 µg daily to 0.25µg three times per week.
D	321 (54%)	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm	*Example:* Frequency change of metformin 500 mg twice daily to 500 mg three times daily.
E	74 (13%)	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention	*Example:* Omission of fenprocoumon 3 mg daily.
F	7 (1%)	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization	*Example:* Omission of prednisolone 5 mg daily.
G	15 (3%)	An error occurred that may have contributed to or resulted in permanent patient harm	*Example:* Omission of tacrolimus 4 mg daily.
H	0	An error occurred that required intervention necessary to sustain life	NA[b]
I	0	An error occurred that may have contributed to or resulted in the patient's death	NA[b]

Potential harm classification according to the National Coordinating Council on Medical Error Reporting and Prevention (NCC-MERP) classification system.[11]

[a] Categories A and B were not applicable in the current study, because in this retrospective study all errors reached the patient.

[b] In the current study no MTE were classified into categories G to I.

The association of patient characteristics (age, sex, number of medications and kidney function) with MTE was analyzed using univariate and multivariate logistic regression. Only parameters with a p-value < 0.20 in the univariate analysis were included in the multivariate model. The results of the logistic regression analysis were reported as odds ratios (OR) and 95%-confidence intervals (95% CI). The number of medications was analyzed as a continuous variable and in four groups to be able to select patient groups.

Interrater reliability of the classification of the potential harm of MTE was analyzed and Cohen's kappa was reported.

RESULTS

During the study period medication reconciliation was performed for 380 patients. Figure 1 shows that after removing duplicates 3615 medications in 380 patients remained for analysis. For 290 medications it remained unclear what the exact use of the medication was after medication reconciliation with the medical assistant. These medications were presented to the nephrologist and discussed during the outpatient visit, and were excluded from the analysis. Characteristics of the included patients are shown in Table 2.

A total of 589 medication transfer errors (MTE) was identified in 235 of the 380 patients (61.8%). An average of 1.55 (±2.28) MTE per patient was found. The number

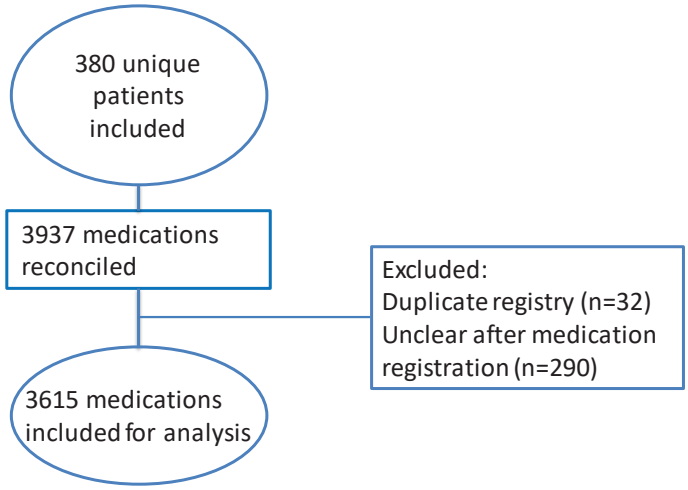

Figure 1. Study flow. The medications that remained unclear were presented to the nephrologist and discussed during the outpatient visit

Table 2. Patient characteristics (n=380)

Characteristics	Mean ± SD / n (%)
Age (years), mean ± SD (range)	53.9 ± 15.7 (20-93)
Male, n (%)	206 (54.2%)
Number of medications, mean ± SD (range)	10.3 ± 4.6 (1-31)
Number of medications in groups, n (%)	
0-4	38 (10%)
5-9	127 (33.4%)
10-14	148 (38.9%)
>14	67 (17.6%)
eGFR (ml/min/1.73m^2) mean ± SD (range)	53.3 ± 23.0 (7-90)

of medications was significantly associated with the occurrence of MTE. Age, sex and kidney function were not significantly associated with MTE (Table 3), but kidney function and age showed an association with a p-value < 0,2. In the multivariate logistic regression model adjusting for age and kidney function only the number of medications remained significant OR 1.10 (95%-CI 1.04-1.16). When analyzing the number of medication in groups, it was shown that using more than 10 medications significantly increases the risk of MTE (Table 3).

Of the 589 MTE, 244 (41%) were omissions, followed by 208 (35%) commissions, and 137 (23%) changes in frequency, dose or route. In Table 1 the potential harm and examples per category of the MTE are shown. Cohen's kappa for the interrater variability was 0.68 which represents a substantial agreement between the two researchers. Medications from the ATC group Alimentary tract and metabolism (20.4%), Cardiovascular system (15.4%) and Nervous system (12.2%) were most often involved in MTE.

DISCUSSION

This study shows that almost two third of nephrology transplant outpatients encounter MTE. This corresponds with literature for outpatient medication reconciliation where 47.6 %[7] to approximately 80%[6,8] of patients were reported to have encountered MTE. The high percentages of MTE in this study can be explained by the high average number of (10.3 +/- 4.6) medications that is used by this patient population. This is in accordance with the systematic review of Hias *et al.*[2] in which the number of medications was found to be the most frequently identified predictor for medication errors.

Age, gender and kidney function were not associated with the occurrence of MTE in this study. However, Hias et al[2] reported that higher age and gender are found to be

Table 3. Association of patient characteristics with medication transfer errors

Parameter	Patients without medication transfer errors (n = 145)	Patients with medication transfer errors (n = 235)	Univariate Odds Ratio (95% CI)	Multivariate Odds Ratio[c] (95% CI)
Age	52.4 ± 15.5	54.9 ± 15.7	1.010 (0.10-1.02)[a]	1.00 (0.99-1.02)
Sex	81 (55.9%)	125 (53.2%)	0.90 (0.59-1.36)	-
Number of medications	9.0 ± 4.3	11.0 ± 4.7	1.11 (1.06-1.17)[b]	1.10 (1.04-1.16)[b]
0-4	22 (15.2%)	16 (6.8%)	N.A. reference group	
5-9	57 (39.3%)	70 (29.8%)	1.69 (0.81-3.51)[a]	1.57 (0.74-3.32)
10-14	50 (34.5%)	98 (41.7%)	2.70 (1.30-5.58)[b]	2.37 (1.10-5.07)[b]
> 14	16 (11.0%)	51 (21.7%)	4.38 (1.87-10.3)[b]	3.80 (1.56-9.24)[b]
Kidney function	55.2 ± 22.7	52.1 ± 23.2	0.99 (0.99-1.00)[a]	1.00 (0.99-1.02)

[a] *p*-value < 0.20
[b] *p*-value < 0.05
[c] In the multivariate model age, number of medications and kidney function were included.

associated with MTE at admission in some studies, albeit within a different population. Stewart et al[10] studied the association between patient characteristics and MTE in an outpatient primary care clinic. Our results are In accordance with the results of Stewart et al[10]. Stewart et al reported patients using three or more medications to be associated with the presence of at least one discrepancy, as compared to patients using one or two medications, while age and gender were not found to be associated with the occurrence of discrepancies.[10] The high number of medications used by and relatively young age of our outpatient population is probably the reason that only the number of medications is associated with MTE.

In the literature renal and cardiovascular medications are most often found to be associated with medication discrepancies in accordance with the findings of this study.[7,8] The potential harm of the MTE in this study was found to be different when compared to earlier studies. In this study 71% of the MTE was assessed as having the ability to cause potential harm or to need intervention to prevent harm. In earlier studies[7,8] this percentage was only 30%. This difference could be explained by the different inclusion criteria used. In this study only the first medication reconciliation results were included for a patient, while the cited studies included multiple results per patient. After the first medication reconciliation the MTE that are found in a later stage are likely to be less harmful.

To our knowledge this is the first study that explores the association of risk factors for MTE in nephrology transplant outpatients. Another strength of this study is the use of data gathered in usual care. No specific patients were excluded, as all patients used medications. However, several limitations need to be mentioned as well. For 290 medications the actual medication use remained unclear even after medication reconciliation. Therefore, the number of MTE identified may be an underestimation. This could be due to the fact that medication reconciliation was performed by a medical attendant, instead of a pharmacist or a pharmacy technician. In earlier studies it has been shown that pharmacy professionals perform medication reconciliation more effectively. [12] However, due to the use of the 'Medical Dashboard' the crucial step of combining medication information from two sources has become automated, making it easier to perform medication reconciliation. Furthermore, the results of this study cannot be extrapolated to all outpatient clinics because the average number of medications in use by this outpatient nephrology transplant population is very high. Therefore, the risk of MTE for this population is high as well. Finally, due to the monocenter design our results may not be applicable to other outpatient nephrology clinics.

Medication reconciliation in ambulatory nephrology transplant patients is clinically relevant. A higher number of medications used is associated with more MTE. Therefore, medication reconciliation is especially important for patients with extensive medication lists. However, medication reconciliation becomes more time consuming when more medications need to be reconciled. Therefore, the potential use of a time saving electronic tool like the 'Medical Dashboard' warrants further study. In current practice it is not feasible to perform medication reconciliation for every outpatient visit with

a structured interview, so it would be interesting to investigate if a tool like the 'Medical Dashboard' would empower patients to perform their own medication reconciliation. If patients are able to perform their own medication reconciliation this could result in less MTE in a time efficient way.

CONCLUSION

Medication transfer errors (MTE) were found in 61.8% of the nephrology transplant outpatients. The number of medications used is significantly associated with the occurrence of MTE. Omissions are the most common (41%) type of MTE. Lastly 71% of the MTE were assessed to cause potential harm or to need intervention to prevent harm.

REFERENCES

1. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ. 2005 Aug 30;173(5):510-5.
2. Hias J, Van der Linden L, Spriet I, Vanbrabant P, Willems L, Tournoy J, et al. Predictors for unintentional medication reconciliation discrepancies in preadmission medication: a systematic review. Eur J Clin Pharmacol. 2017 Nov;73(11):1355-1377.
3. Mekonnen AB, Abebe TB, McLachlan AJ, Brien JA. Impact of electronic medication reconciliation interventions on medication discrepancies at hospital transitions: a systematic review and meta-analysis. BMC Med Inform Decis Mak. 2016 Aug 22;16:112.
4. Leguelinel-Blache G, Arnaud F, Bouvet S, Dubois F, Castelli C, Roux-Marson C, Ray V, Sotto A, Kinowski JM. Impact of admission medication reconciliation performed by clinical pharmacists on medication safety. Eur J Intern Med. 2014 Nov;25(9):808-14.
5. Richtlijn Overdracht van medicatiegegevens in de keten. Cited 07 May 2018.
6. van der Gaag S, Janssen MJA, Wessemius H, Siegert CEH, Karapinar-Çarkit F. An evaluation of medication reconciliation at an outpatient Internal Medicines clinic. Eur J Intern Med. 2017 Oct;44:e32-e34.
7. Wilson JS1, Ladda MA2, Tran J3, Wood M4, Poyah P5, Soroka S6, Rodrigues G2, Tennankore K7. Ambulatory Medication Reconciliation in Dialysis Patients: Benefits and Community Practitioners' Perspectives. Can J Hosp Pharm. 2017 Nov-Dec;70(6):443-449. Epub 2017 Dec 21.
8. Phillips M, Wilson JA, Aly A, Wood M, Poyah P, Drost S, Hiltz A, Carver H. An Evaluation of Medication Reconciliation in an Outpatient Nephrology Clinic. CANNT J. 2017 Apr-Jun;26(2):29-33.
9. Gleason KM, McDaniel MR, Feinglass J, Baker DW, Lindquist L, Liss D, Noskin GA. Results of the Medications at Transitions and Clinical Handoffs (MATCH) study: an analysis of medication reconciliation errors and risk factors at hospital admission. J Gen Intern Med. 2010 May;25(5):441-7. doi: 10.1007/s11606-010-1256-6. Epub 2010 Feb 24.
10. Stewart AL1, Lynch KJ. Identifying discrepancies in electronic medical records through pharmacist medication reconciliation. J Am Pharm Assoc (2003). 2012 Jan-Feb;52(1):59-66. doi: 10.1331/JAPhA.2012.10123.
11. National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP). Types of Medication Errors. NCCMERP national coordinating council for medication error reporting an prevention, 20011996. http://www.nccmerp.org/types-medication-errors. Updated 2001. Accessed April 2018.
12. Mekonnen AB, McLachlan AJ, Brien JA. Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis. J Clin Pharm Ther. 2016 Apr;41(2):128-44.

CHAPTER

8

THE EFFECT OF MEDICATION RECONCILIATION VIA A PATIENT PORTAL ON MEDICATION DISCREPANCIES; A RANDOMIZED NON-INFERIORITY STUDY

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ABSTRACT

Medication reconciliation (MR) has become standard care to prevent medication transfer errors. However, this process is time-consuming and may become more efficient when patients are engaged in medication reconciliation via a patient portal.

Objectives

To explore whether medication reconciliation by the patient via a patient portal is non-inferior to medication reconciliation by a pharmacy technician.

Design (including intervention)

Open randomized controlled non-inferiority trial. Patients were randomized between medication reconciliation via a patient portal (intervention) or medication reconciliation by a pharmacy technician at the preoperative screening (usual care).

Setting and Participants

Patients scheduled for elective surgery using at least one chronic medication were included.

Measures

Primary endpoint was the number of medication discrepancies compared to the electronic nationwide medication record system (NMRS). Secondary, time investment of the pharmacy technician for the medication reconciliation interview and patient satisfaction were studied. Non-inferiority was analysed with an independent T-test, and the margin was set at 20%.

Results

A total of 499 patients were included. The patient portal group contained 241 patients; the usual care group contained 258 patients. The number of medication discrepancies was 2.6 ± 2.5 in the patient portal group and 2.8 ± 2.7 in the usual care group. This was not statistically different and within the predefined non-inferiority margin. Patients were satisfied with the use of the patient portal tool. Also, the use of the portal can save on average 6.8 minutes per patient compared to usual care.

Conclusions and Implications

Medication reconciliation using a patient portal is non-inferior to medication reconciliation by a pharmacy technician with respect to medication discrepancies, and saves time in the medication reconciliation process. Future studies should focus on identifying patient characteristics for successful implementation of patient portal medication reconciliation.

INTRODUCTION

Medication reconciliation has become standard of care to prevent medication transfer errors.[1,2] It is defined as the process of creating the Best Possible Medication History (BPMH) of all drugs, including dose, frequency and administration route. The BPMH is compared to the admission medication and any unintended discrepancies are resolved. In the Dutch guideline on medication transfer, medication reconciliation is required in all transitions of care within 24 hours.[3]

Despite this guideline, the number of medication discrepancies in patient transfers is high.[2] This number can be substantially reduced when medication reconciliation is performed by dedicated pharmacy staff.[4,5] Pharmacy-led medication reconciliation reduced the proportion of patients with medication discrepancies by 66%.[4] A meta-analysis on pharmacist-led interventions in medication reconciliation showed a decrease in medication discrepancies of 42%.[5]

However, performing medication reconciliation is a time consuming process. The patient interview at admission takes 12-16 minutes per patient.[6] The entire process of medication reconciliation takes a median of 50 minutes per patient.[6] Therefore, implementing pharmacy led medication reconciliation may be hampered by budgetary constraints within hospitals or other healthcare facilities. One solution to lower the costs is the deployment of pharmacy technicians instead of pharmacists.[7]

Engaging the patient in medication reconciliation could further contribute to cost containment by making the medication reconciliation process less time consuming. Several studies have shown that patients can have a role in medication reconciliation, although often resulting in incomplete medication lists.[8,9] This generally improves when the patient is presented a medication list and is asked to adjust and supplement that list. Medication lists may be presented to patients via a patient portal, after which the medication reconciliation by the patient can be performed electronically.[10-13] Patients are generally satisfied with using the patient portal and think that it could improve communication about medication with healthcare professionals.[12]

Although these studies show that patients can have a role in medication reconciliation, to our knowledge no studies have been performed in which the quality of patient portal medication reconciliation was compared to medication reconciliation by a pharmacy professional.

Therefore, the aim of this study is to explore whether medication reconciliation by the patient via a patient portal is non-inferior to medication reconciliation by a pharmacy technician, with respect to the number of medication discrepancies.

METHODS

Study design

This prospective open randomized controlled non-inferiority study was conducted at the preoperative screening appointment. Medical ethical approval of the study was

granted by the Medical Ethical Committee of the hospital. Patients were contacted by telephone at least one week prior to the preoperative screening appointment to ask if they were willing and able to participate in the study. Patients were randomly assigned to the intervention group or control group. The randomization list was created by an independent trial coordinator using Microsoft Excel's (2010) data randomizer function in blocks of 200 patients. Due to the nature of the intervention patients and pharmacy technicians were not blinded. The patients in the intervention group were invited to use the electronic patient portal medication reconciliation system (eMR) one week prior to the preoperative screening appointment. The patients in the control group received usual care in which medication reconciliation (MR) was performed at the preoperative screening appointment by pharmacy technicians. Since the quality of the patient portal medication reconciliation was yet unknown, medication reconciliation by a pharmacy technician was repeated in all intervention patients after they had completed the reconciliation in the patient portal.

Study population

All patients of 18 years and older with an appointment at the preoperative screening and used at least one medication were eligible for inclusion. Patients were included between September 2018 and February 2020. Patients who were not able to communicate in Dutch and patients who were not able to perform medication reconciliation on an electronic device were excluded.

Usual care

The usual care medication reconciliation process at the preoperative screening appointment consisted of several steps. First, the community pharmacy medication dispensing list was retrieved through the electronic Nationwide Medication Record System (NMRS).[14] Second, this list was combined with the medication in the hospital electronic patient record. Subsequently, every medication on the combined medication list was discussed with the patient in a face-to-face interview to establish current dosage and use. Using a checklist (appendix 1), the patient was explicitly asked for any missing medication and for specific over the counter medication. The result of the medication reconciliation was the best possible medication history (BPMH).

Intervention

The patient portal was developed by Zorgdoc® (Zorgdoc, Zorgdoc Nederland BV, Eindhoven, The Netherlands). The medication reconciliation application in the patient portal was developed in cooperation with health care professionals and patients to make the application user friendly. Some hospitals in the Netherlands already use the patient portal.[15] The patient portal consists of a protected digital environment in which a patient can log in and is guided through the steps of medication reconciliation. The patient

portal uses both the NMRS and the medication available in the hospital electronic patient record (Hix, Chipsoft B.V., Amsterdam, The Netherlands) as a starting point for medication reconciliation. These medications are shown in comprehensive blocks (Figure 1). For each medication the patient can confirm the use, adjust the dose/frequency, indicate not using it at all, or not recognizing the medication. After this the patient is offered the opportunity to add medication. Furthermore, the standard questions (if patients use any over the counter medication, medication that is used less frequently or with different administration routes) are also asked in the patient portal. Due to the fact that patients were able to add medication as 'free text' a validation step was included in which a researcher checked the data for impossibilities and updated the medication in the hospital electronic record.

Outcome measures

The primary outcome was the number of medication discrepancies compared to the NMRS. This primary outcome was chosen due to the nature of the intervention. Ideally, the BPMH is the gold standard to which the results of medication reconciliation

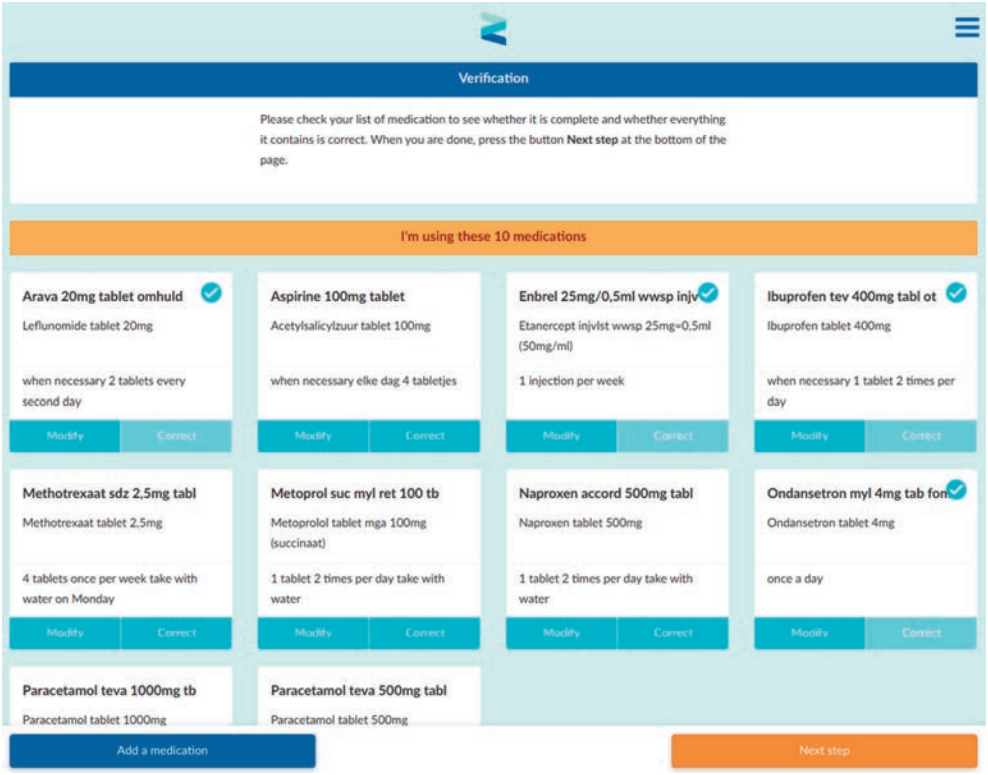

Figure 1. Screen shot of the patient portal 'Zorgdoc'.

should be compared. However, in our situation it would be impossible to obtain a BPMH in the same patient without introducing recall bias. The NMRS is not optimal, but by using it in both groups as the comparator, no bias will be introduced.[14] Therefore, a medication discrepancy was defined as any difference between the medication list resulting from the eMR or MR, with the NMRS. The discrepancies were classified as omission (not on the NMRS but on the (e)MR), commission (on the NMRS but not on the (e)MR), or dose/frequency change.

Secondary outcomes were the time investment of the pharmacy technician for the medication reconciliation in the MR group compared to the eMR group and the patient satisfaction with the patient portal medication reconciliation or usual care was reported. Time investment of patients fulfilling the eMR was also reported.

Data collection

The following patient characteristics were collected from the patient record: age, gender, medical specialty, and comorbidities. Data from the medication reconciliation process were collected: number of medications on NMRS, number of medications after (e)MR, number of discrepancies between NMRS and result of (e)MR. For every discrepancy, medication name, dose, frequency, type of discrepancy (omission, commission or dose/frequency change), and Anatomic Therapeutic Chemical (ATC) code were collected. Furthermore, in both groups patient satisfaction was determined using a questionnaire with 3-6 statements with a visual analogue scale (VAS) from 1-10.

All patients scored the following three statements: I (would) like to do my medication reconciliation from home, I am satisfied with the medication reconciliation method, I prefer the medication reconciliation in the hospital. The second statement was used to determine overall satisfaction with the medication reconciliation method. For the eMR group another three statements were scored: The patient portal was easy to use, I felt confident using the patient portal, It took me some time to get going with the patient portal. For eMR patients the questionnaire was shown after completing the medication reconciliation process in the electronic tool. Patients in the usual care group received the questionnaire on paper after the MR interview and were asked to fill out the questionnaire in the waiting room. When patients reported technical or medication related issues this was also recorded. The time investment of the medication reconciliation interview by the pharmacy technician was calculated by recording the start and end time of the interview on the study form. Finally, the time to complete the eMR was automatically collected.

Data monitoring

All data were collected in OpenClinica version 3.12.2 (OpenClinca LLC, Waltham, MA). Data were processed by a researcher and 10% of the data was checked by another researcher and compared to the patient record, if any error was discovered another

10% of the data was checked for errors. This was repeated until no errors were found or all data were checked. Furthermore, after finishing the data collection in OpenClinica the data were checked for missing and impossible values and corrected. After correction, the database was locked and extracted for analysis.

Data analysis

The sample size calculation was based on a non-inferiority design with a non-inferiority margin of 20% resulting in an absolute margin of 0.6 based on literature and clinical practice using an unpaired T-test.[1] In a three-day analysis of the medication reconciliation results at the preoperative screening on average 3.8 medication discrepancies were seen with a standard deviation of 3.7. With a power of 0.8 and alpha of 0.05 a sample size of 470 patients per group was calculated. However due to the short period of measurement the standard deviation was very high and an interim analysis after the first 200 patients was used to calculate the standard deviation and recalculate the sample size with an alpha of 0.025 to correct for multiple testing. This recalculated sample size using an alpha of 0.025 resulted in a group size of 234 per group.

Data analysis was performed using IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY). The number of discrepancies in the two groups were compared using an unpaired two sample T-Test. An intention to treat and a per protocol analysis were performed. In the intention to treat analysis the median number of medication discrepancies was used to estimate the missing results of the patients lost to follow up. The mean difference with 95% confidence interval was reported. Secondary endpoints were reported using descriptive statistics. Overall patient satisfaction with the method of medication reconciliation was tested using an unpaired two sample T-test.

RESULTS

Between September 2018 and February 2020, 2226 patients visited the preoperative screening. In total, 598 patients were randomized, 300 to the electronic medication reconciliation and 298 to the usual care group. Figure 2 shows numbers of eligible patients and reasons for exclusion. 99 patients were lost to follow up, therefore 499 patients were included in the analysis. Of the 99 patients lost to follow up 29 patients that were randomized to eMR did not complete the patient portal eMR, 8 due to technical reasons, 2 patients because they tried but were not able to, and 19 unknown. These 29 patients did not differ significantly in patient characteristics from the rest of the study population. No data on medication discrepancies are available for these patients. Table 1 shows the baseline characteristics of the 499 patients of which a primary endpoint can be reported.

The 990 excluded patients were significantly older on average 62.2 ± 14.9 and 42% male.

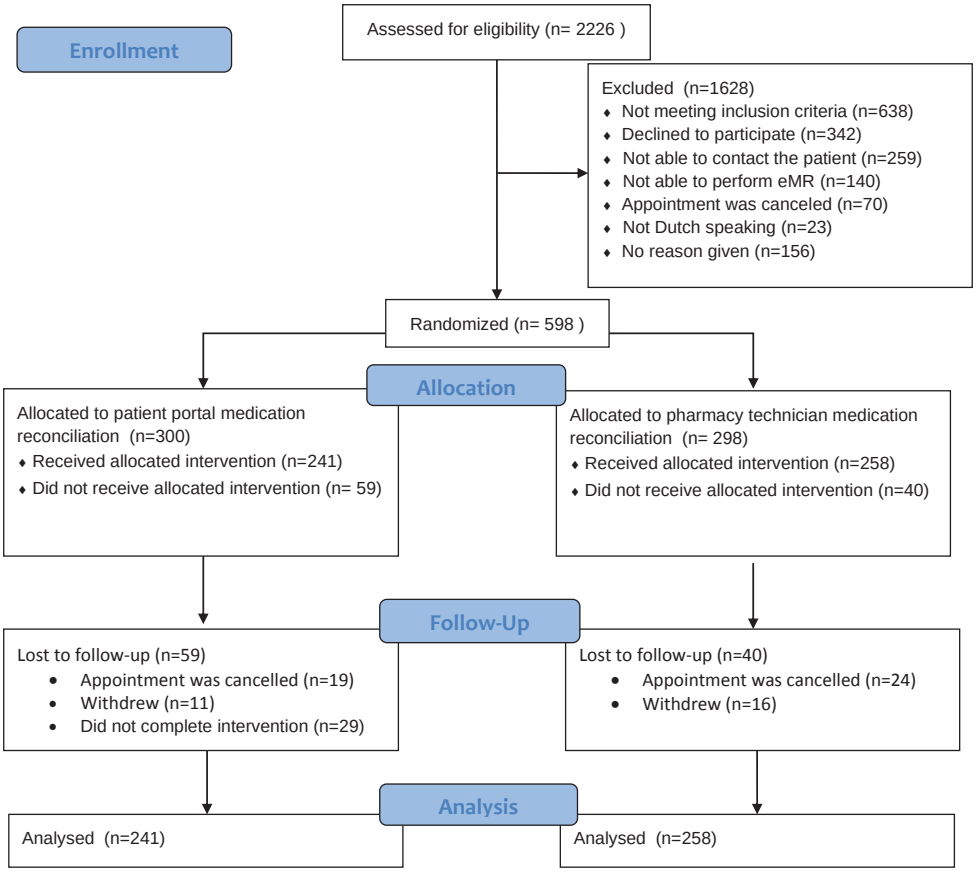

Figure 2. Study flow

Table 1. Baseline characteristics

	MR (n=258)	eMR (n=241)
Age, mean ± sd	58.6 ± 14.2	58.9 ± 13.9
Sex male, n (%)	120 (46.5%)	120 (49.8%)
Number of medications before MR, mean ± sd	5.9 ± 3.9	5.1 ± 3.3
Number of medications after MR, mean ± sd	6.7 ± 4.5	6.1 ± 3.9
Comorbidities		
Hypertension, n (%)	110 (42.6%)	105 (43.6%)
Cardiac disease, n (%)	87 (33.7%)	82 (34.0%)
Asthma/COPD, n (%)	43 (16.7%)	33 (13.7%)
Blood disease, n (%)	32 (12.4%)	24 (10.0%)
Diabetes mellitus, n (%)	43 (16.7%)	33 (13.7%)
Stomach problems, n (%)	51 (19.8%)	45 (18.7%)
CVA/stroke, n (%)	23 (8.9%)	20 (8.3%)

The mean number of medication discrepancies in the eMR group was 2.6 ± 2.5 and 2.8 ± 2.7 in the MR group. The absolute difference of 0.2 is smaller than the predefined non-inferiority margin of 0.6. in addition, the difference was not statistically significant in the per protocol analysis (mean difference -0.23; 95% CI -0.69-0.22). In the intention-to-treat analysis (300 eMR and 298 MR) with an estimated number of discrepancies of 2 (the median in both groups) the mean number of discrepancies were 2.5 ± 2.3 and 2.7 ± 2.5, respectively. The difference between the 2 groups was also not statistically significant (mean difference -0.24; 95% CI -0.62-0.15).

Patient satisfaction

The response to the questionnaire was 97% (n=233) in the eMR group and 79% (n=203) in the MR group. Patients in the usual care group were more satisfied with the MR method than patients in the eMR group, this was statistically different (mean difference -0.6; 95%-CI -0.8—0.3). With an average of 8.7 and 8.1 respectively both methods have high patient satisfaction. Patients in the eMR group assessed the patient portal as easy to use and felt confident using the system, although they needed some time to get going with the patient portal (Figure 3). Both patient groups prefer medication reconciliation from home compared to the hospital, but the difference is larger in the eMR group (Figure 4).

Time investment for medication reconciliation interview

For 234 patients in the eMR group and 210 patients in the MR group data on duration of the medication reconciliation (eMR) or patient interview (MR) were available. The average

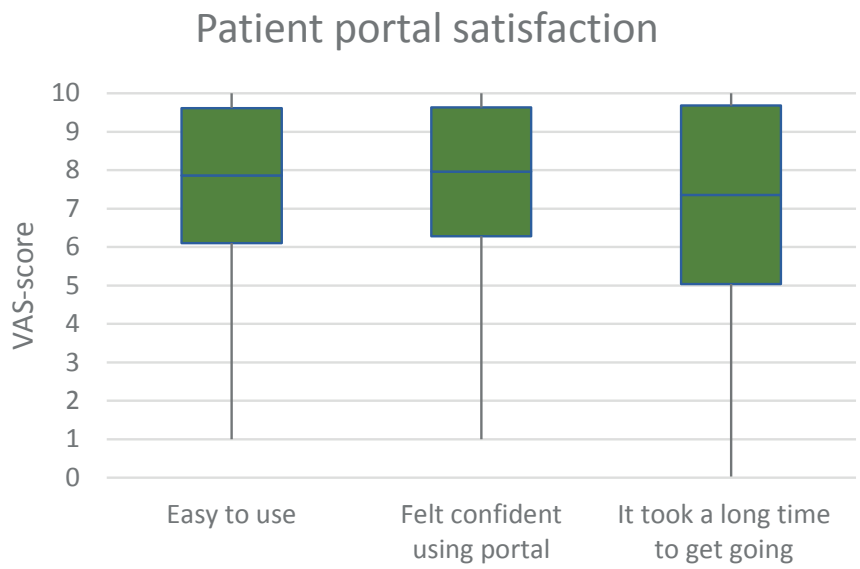

Figure 3. Patient portal satisfaction. Per statement mean ± standard deviation are shown within the box, upper and lower limit with lines.

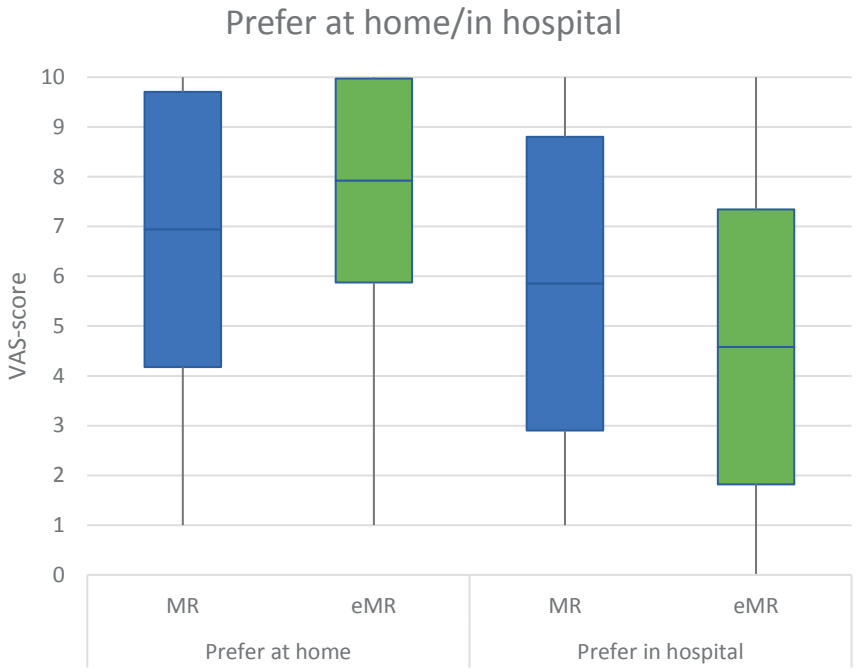

Figure 4. Patient preference about the location of the medication reconciliation (MR). For each statement mean ± standard deviation are shown within the box, upper and lower limit with lines. Blue = usual care (MR), green = patient portal medication reconciliation (eMR).

time for the patient to complete the electronic medication reconciliation tool including the patient satisfaction questionnaire was 14.9 ± 13.8 minutes. The average time for the pharmacy technician to perform the medication reconciliation interview was 7.8 ± 5.2 minutes. The average time for the researcher to validate the results from the eMR tool for all eMR patients was 1 minute. In this study data from the electronic tool needed to be transferred to the electronic hospital record, this took 3.9 min ± 2.3. Medication reconciliation with the electronic tool saved on average 2.9 minutes per patient and if information could be automatically transferred to the hospital system this could save on average 6.8 (2.9 + 3.9) minutes per patient.

DISCUSSION

This study shows that medication reconciliation with a patient portal is non-inferior to medication reconciliation by a pharmacy technician. Earlier studies have shown that patient portal medication reconciliation is feasible but did not compare it with usual care.[10-13]

Unfortunately, at the time this study was performed it was not possible to link the results of the electronic medication reconciliation to the electronic hospital record.

Therefore, the researcher verified the result of the patient portal medication reconciliation and manually transferred the medication overview to the electronic hospital record. Ideally, when implementing the patient portal medication reconciliation the automatic transfer is also implemented saving more time. However, even when medication needs to be transferred manually the patient portal medication reconciliation still saves time.

Patients were generally satisfied with the patient portal medication reconciliation method, compared to earlier results.[11,12] Although patients in the usual care group were significantly more satisfied with the medication reconciliation method than patients in the patient portal group, the difference was small. Both patient groups indicated that they preferred medication reconciliation at home above medication reconciliation in the hospital. This indicates that patients are willing to perform medication reconciliation at home although patients are more satisfied with the face-to-face medication reconciliation interview in the hospital.

Limitations and strengths

To our knowledge this is the first randomized study comparing medication reconciliation via a patient portal with usual care. Using the application in a daily clinical setting has proven that a patient portal can be implemented in clinical practice in at least a subgroup of patients.

Due to the informed consent procedure before inclusion in the study patients may not be representative for the general population. It could be that more educated patients are more likely to consent to the study, but data on socio-economic status or educational level were not collected. The patients who did not participate were on average 3.5 years older than included patients. This is also seen in the study of Witting et al where the ability of self-reporting medication decreases with increasing age.[8] However, in a systematic review Jonker et al. concluded that older (>65 years) surgical patients consider eHealth interventions to be feasible.[16] Also, of the 270 patients randomized to the patient portal medication reconciliation, 29 did not use the application. This illustrates that a patient portal tool will never be suitable for every patient and alternative ways to perform medication reconciliation will still be needed. However, patients that used the electronic medication reconciliation are very satisfied with the use of the patient portal.

Furthermore, patients in the patient portal group performed their medication reconciliation at home and therefore had access to their medication bottles or boxes. When performing medication reconciliation in the hospital the medication bottles or boxes are not available. Therefore, the patient portal medication reconciliation might be more accurate than the control. However, the current gold standard medication reconciliation in the Netherlands does not include medication bottles[17]

Finally, this study is performed in the Netherlands with use of the nationwide medication record system (NRMS). Not all countries have such a system, therefore the results in this study might not be generalizable to all countries. However, the patient

portal medication reconciliation can always be used with electronic medication records from the own hospital.

Implications for future research

This study showed that medication reconciliation via a patient portal is non-inferior to usual care medication reconciliation. After completing this study, the digitization of healthcare has accelerated due to the Covid-19 pandemic. To minimize face-to-face contact during the pandemic, alternative ways to perform medication reconciliation are needed. This study has shown that a patient portal medication reconciliation is non-inferior to a face-to-face interview and can therefore be safely used in situations where in-person contact needs to be avoided. How many patients will be able to use this method remains to be determined in clinical practice. Implementation studies exploring barriers and facilitators for use of a patient portal are needed in order to maximize the feasibility of this time efficient intervention.

8 CONCLUSION AND IMPLICATIONS

Medication reconciliation using a patient portal is non-inferior to medication reconciliation by a pharmacy technician and saves time in the medication reconciliation process.

The authors declare no conflicts of interest.

REFERENCES

1. Mekonnen AB, Abebe TB, McLachlan AJ and Brien JE. Impact of electronic medication reconciliation interventions on medication discrepancies at hospital transitions: a systematic review and meta-analysis. BMC Medical Informatics and Decision Making 2016;16:112. doi: 10.1186/s12911-016-0353-9.
2. Tam VC, Knowles SR, Cornish PL, Fine N, et al. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ 2005;173(5):510-515. doi: 10.1503/cmaj.045311
3. Dutch Federatie Medisch Specialisten and Ministry of Health Welfare and Sports. Leidraad Overdracht van Medicatiegegevens in de keten.
4. Mekonnen AB, McLachlan AJ, and Brien JA. Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis. J Clin Pharm Ther 2016;41(2):128-144. doi: 10.1111/jcpt.12364
5. Cheema E, Alhomoud FK, Kinsara ASAL- D, Alsiddik J, et al. The impact of pharmacists-led medicines reconciliation on healthcare outcomes in secondary care: A systematic review and meta-analysis of randomized controlled trials. PLoS ONE 2018;13(3). doi:10.1371/journal.pone.0193510.
6. Hammad EA, Bale A, Wright DJ, and Bhattacharya D. Pharmacy led medicine reconciliation at hospital: A systematic review of effects and costs. Res Social Adm Pharm 2017;13(2):300-312. doi: 10.1016/j.sapharm.2016.04.007.
7. Johnston R, Saulnier L and Gould O. Best possible medication history in the emergency department: comparing pharmacy technicians and pharmacists. Can J Hosp Pharm. 2010; 63(5):359-365. doi: 10.4212/cjhp.v63i5.947.
8. Witting MD, Hayes BD, Schenkel SM, Drucker CB, et al.. Emergency department medication history taking: current inefficiency and potential for a self-administered form. The Journal of Emergency Medicine 2013;45(1):105–110. doi: 10.1016/j.jemermed.2013.01.019.
9. Lee KP, Nishimura K, Ngu B, Tieu L, et al. Predictors of completeness of patients' self-reported personal medication lists and discrepancies with clinic medication lists. Annals of Pharmacotherapy 2014;48(2):168–177. doi: 10.1177/1060028013512109.
10. Heyworth L, Paquin AM, Clark J, Kamenker V, et al. Engaging patients in medication reconciliation via a patient portal following hospital discharge. J Am Med Inform Assoc. 2014;21(e1):e157-162. doi: 10.1136/amiajnl-2013-001995
11. Kripalani S, Roumie CL, Dalal AK, Cawthon C, et al. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial. Ann Intern Med. 2012;157(1):1–10. doi: 10.7326/0003-4819-157-1-201207030-00003.
12. Marien S, Legrand D, Ramdoyal R, Nsenga J, et al. A web application to involve patients in the medication reconciliation process: a user-centered usability and usefulness study. Journal of the American Medical Informatics Association 2018;25(11):1488–1500. doi: 10.1093/jamia/ocy107.
13. Prey JE, Polubriaginof F, Grossman LV, Creber, RM, et al. Engaging hospital patients in the medication reconciliation process using tablet computers. Journal of the American Medical Informatics Association 2018;25(11):1460–1469. doi: 10.1093/jamia/ocy115

14. Uitvlugt EB, van den Bemt BJF, Chung WL, Dik J, et al. Validity of a nationwide medication record system in the Netherlands. Int J Clin Pharm 2019;41(3):687-690. doi: 10.1007/s11096-019-00839-x.

15. Eérst online check medicatie, dán consult bij reumatoloog, Pharmaceutisch Weekblad 2017;152:8-9

16. Jonker LT, Haveman ME, de Bock GH, van Leeuwen BL et al. Feasibility of perioperative ehealth interventions for older surgical patients: a systematic review. JAMDA 2020;S1525-8610(20)30438-2. doi: 10.1016/j.jamda.2020.05.035.

17. van der Nat DJ, Taks M, Huiskes VJB, van den Bemt BJF, et al. A comparison between medication reconciliation by a pharmacy technician and the use of an online personal health record by patients for identifying medication discrepancies in patients' drug lists prior to elective admissions. Int J Med Inform. 2021;147:104370. doi: 10.1016/j.ijmedinf.2020.104370. Epub 2020 Dec 29.

PART III

GENERAL DISCUSSION, SUMMARY AND APPENDICES

CHAPTER

9

GENERAL DISCUSSION

GENERAL DISCUSSION

Medication reconciliation is a safety intervention that has proven to prevent medication transfer errors.[1, 2] Due to the lack of an integrated nationwide electronic medication record, medication reconciliation is necessary to gain insight into the current medication use and prevent medication transfer errors. However, medication reconciliation is time-consuming and therefore improving efficiency in medication reconciliation is necessary to decrease costs.[3, 4] The overall aim of this thesis was to explore ways to improve efficiency in medication reconciliation. In this general discussion, the main results of this thesis are discussed in a wider perspective and the results are compared to existing literature.

RISK FACTORS

In this thesis we identified risk factors of medication transfer errors enabling us to select patients at high risk and perform a less intensive medication reconciliation procedure in low-risk patients. In the systematic review we showed that various studies identified the number of medications a patient uses as a risk factor of medication errors at transitions of care. This can be explained by pure chance, the more medications in use, the higher the chance that a discrepancy occurs in one of the medications. A higher efficiency is difficult to gain in low risk patients who use less medications, because medication reconciliation already is less time consuming than for patients who use more medications. Furthermore, with the general population getting older with multimorbidity and consequently a rising average medications in use, the low risk patient group in the hospital setting will get smaller. A part of the problem in the failure to find more robust risk factors can be the large heterogeneity in the reported studies. In addition, new studies tend to repeat looking at risk factors found in earlier studies instead of looking for new risk factors. There are probably better prediction factors of medication errors not yet identified. The heterogeneity of studies and the use of artificial intelligence to find new risk factors are discussed below.

Heterogenous study design

The circumstances and patient characteristics in the study designs of reported studies about medication reconciliation are different. The studies differ between medical specialties, admission type (elective, acute) and patient age. Also, different studies have different methods of performing medication reconciliation and different healthcare professionals that perform medication reconciliation. It is possible that within all these different patient populations and settings different types of risk factors are associated with medication transfer errors. When the setting influences the risk factors future reviews should focus on studies in the same setting. However, in our systematic review we did not find the same risk factors even in studies that included the same population, as also shown in Chapter 4 and 5.[5, 6] This may be due to the fact that the populations were not

completely the same, but only 'comparable'. Thus the advice to focus on truly comparable settings is still valid.

Furthermore, the primary endpoint in studies differ as to the definition of a medication transfer error. In general, it can be defined as a medication discrepancy between the medication list the doctor composes and the gold standard, which is the best possible medication history (BPMH).

But those medication discrepancies may be either intentional or unintentional, and intentional discrepancies should not be included in the definition of a medication transfer error. Yet, in literature this distinction is not always made. This lack of consensus on the definition of a medication error makes comparing risk factors of medication errors even more difficult. At discharge the heterogeneity of the primary endpoint is even larger. The BPMH is compared to primary physician records, hospital discharge letters or medication lists at the first outpatient clinic visit after discharge which makes it even harder to find robust risk factors from different studies. In addition, the definition of medication is not always the same. In some studies medication is defined as only prescription medication where in other studies over-the-counter medication is also included.

Thus, future studies should focus more on a particular care setting with unambiguous definitions of medication errors and include more patient characteristics to be able to create more robust risk prediction models including characteristics not yet identified as potential risk factors to predict patients at high risk of medication transfer errors.

Artificial intelligence to identify new risk factors

Artificial intelligence has shown to be able to identify new risk factors in different fields. The machine learning techniques used in artificial intelligence models enable decision support without a pre-specific hypothesis. Therefore, these machine learning techniques can be used to identify new risk factors.[7] In the prediction of readmissions of heart failure patients it has been shown that a machine learning model predicts readmissions better than earlier models based on logistic regression.[8] In a systematic review by Mahmoudi et al. it is concluded that machine learning models based on electronical medical records predict readmissions better than logistic regression models.[9] Thus, artificial intelligence should be used in future research to evaluate all available data in patient records in order to identify new risk factors. However, when using artificial intelligence with machine learning models it is very important for clinicians to understand the model and to validate the results. In the end, machine learning models can only be as good as the information in the training set to create the model.[10]

MEDICATION RECONCILIATION WITH ELECTRONIC TOOLS AND DEPLOYMENT OF OTHER HEALTHCARE PROFESSIONALS

It is established that pharmacy professionals deliver higher quality medication overviews after performing medication reconciliation compared to other healthcare professionals.[11, 12] However, it is not feasible to have medication reconciliation performed by a pharmacist in every patient. Fortunately, Champion et al. found that trained pharmacy technicians and pharmacy students can perform medication reconciliation with the same accuracy and time efficiency as pharmacists, decreasing costs.[13] In the Netherlands it is already common practice that medication reconciliation is performed by trained pharmacy technicians. In Chapter 6 we showed that in patients at the preoperative screening using 0 or 1 medications medication reconciliation can be performed by the anesthesiologists.[14] This can reduce costs because it is performed during a routine visit to the anesthesiologist. Although patients are getting older and are using more medication, in the current situation 27 to 30% (data from Chapter 4 and 5) of patients use one medication or no medication at all.[5, 6] In the Netherlands in 2017 1.6 million operations were performed, so even if this percentage decreases in the future to 20 or even 10% this still can lead to substantial cost savings.[15] Champion et al. also showed that using electronic tools to facilitate the medication reconciliation process makes it even more cost-effective.[13] When using electronic tools to facilitate the medication reconciliation process and to integrate medication information from different sources, the medication reconciliation process becomes less challenging. We showed in Chapter 7 that with the use of an electronic tool integrating medication information from different sources a trained medical attendant was able to perform medication reconciliation.[16] A study of Hursky et al. already showed that accuracy of medication reconciliation increases when comprehensive electronic tools are used.[17] Tamblyn et al. showed that using an e-medication reconciliation application, RightRx that integrates medication information from different sources improves the number of patients where medication reconciliation is performed.[18] However, Lesselroth et al. studied an electronic medication reconciliation versus a paper based medication reconciliation method and found no difference in medication accuracy. Although they expected that introducing medication images in the electronic medication reconciliation would increase the medication accuracy this did not improve the quality.[19] Further research is needed to establish if the usage of an electronic tool ensures that the quality of this medication reconciliation is as good as or better than the current gold standard pharmacy-led medication reconciliation. Furthermore, when optimizing electronic tools the medication reconciliation may be performed by other healthcare professionals with the same quality because the tool can aid the process. To establish this, randomized controlled trials using electronic tools by pharmacy professionals compared to other healthcare professionals are warranted.

PATIENT INVOLVEMENT IN MEDICATION RECONCILIATION

Patients in patient portal medication reconciliation

Earlier studies have shown that patients are generally satisfied with performing their own medication reconciliation and are also more involved in their own medication use when performing their own medication reconciliation.[20, 21] In Chapter 8 we showed that medication reconciliation by the patient is non-inferior to medication reconciliation by a pharmacy technician.[22] This is an important finding, because it may save substantial amounts of time in the medication reconciliation process. In addition, we showed that patient involvement in medication reconciliation is possible and patients are generally satisfied with performing their own medication reconciliation. We need to realize, however, that it was a randomized controlled trial, where patients needed to agree to participate before they knew in which group they were randomized. It is possible that participants of this study were more motivated to perform their own medication reconciliation than a random sample of patients (selection bias). Of the included patients more than 90% performed their own medication reconciliation without any problems, which is likely to be lower in a non-selected population. Future research needs to establish which patients in daily practice are able to perform their own medication reconciliation. There will be a group of patients, for example illiterate patients or patients with low health literacy, that will not be able to perform their own medication reconciliation. This group must also be taken into account when introducing patient portal medication reconciliation. It would be desirable to develop a patient portal tool that can distinguish between patients that are able to perform their own medication reconciliation and patients that are not able to. Low health literacy can be a reason that patients are not able to provide the necessary information about their medication use simply because they do not understand the information themselves. Different screening tools to identify low health literacy patients are available and it could be useful to integrate such a tool in a patient portal medication reconciliation where low (health) literacy patients are contacted extra to verify the results of the medication reconciliation.

Different levels of patient and family engagement strategies are defined in improving medication safety.[23] Future research on patient portal medication reconciliation should integrate identifying low health literacy and illiterate patients with evaluating the appropriate patient engagement strategies per patient group to improve medication safety by engaging the patient at an appropriate level. Eventually, optimizing medication reconciliation tools can have a double advantage in improving medication safety and saving time from health care professionals.

Healthcare professionals in patient portal medication reconciliation

In Chapter 8 we showed that patient portal medication reconciliation can save time for healthcare professionals because patients perform part of the medication reconciliation

process themselves. A study on the use of patient portal medication reconciliation in Amsterdam academic medical center in the Netherlands in 2018 reported that it is essential that both patients and healthcare professionals are involved in the development of patient portal medication reconciliation.[24] Patient portal medication reconciliation will always need a validation step by a healthcare professional to prevent typing errors in dosages or medication which can lead to unintended medication errors introduced by patients. The medication information in the patient portal medication reconciliation tool should therefore be as complete as possible, so that the patient has to enter as little as possible by him/herself. This decreases the risk of introducing medication errors in the process. Therefore, the validation step and transfer of the medication information into the electronic patient record should also be automated and validated. Under this condition patient portal medication reconciliation can save time for healthcare professionals. In Chapter 8 we showed that if only the validation step is needed and the transfer of information into the health record would be automated this could save 6.8 minutes on average per patient. In 2017 1.6 million clinical admissions occurred in the Netherlands.[15] Under the assumption that half of the clinical admissions is elective, introducing patient portal medication reconciliation could save 6.8 minutes * 800,000 = 5,440,000 minutes = 90,666 hours per year. One full-time (FTE) pharmacy technician translates to 1550 workable hours per year. Which means that introducing this in the Netherlands could save 58 FTE pharmacy technician. With an average yearly cost of 55,000 euro/FTE pharmacy practitioner this could save 3.2 million euro per year.

Government and regulations in patient portal medication reconciliation

In recent years, Dutch government is facilitating improvements in digital information exchange, because this will likely contribute to the quality of care. To this purpose, grants are made available for hospitals under the name VIPP-program.[25] One of the aims of this program is to set up a patient portal in which digital medical data are made available for patients in a standardized way. Furthermore, the basic medical data set in this patient portal should be made available for digital exchange between institutions. In the end, every hospital in the Netherlands, should achieve these two goals. An optional module is the potential for patients to send back data through the patient portal to the healthcare institution.[25] This last option is necessary to make patient portal medication reconciliation available. The advantage of this program is that there are guidelines on how to make the data available and if every hospital implements these guidelines data can be easily transferred from one hospital to another. Unfortunately, the regulations only apply to hospitals while patients spend most of the time at home or in a long-term care facility. To optimize patient portal medication data exchange not only hospitals should participate but all healthcare professionals such as general practitioners, community pharmacists and long-term care facilities. Also, medication information about over-the-counter medication use should be integrated in this system to complete the medication overview.

WHAT SHOULD WE CHANGE IN DAILY PRACTICE LEARNING FROM THIS THESIS

In this thesis we showed that there are different ways to improve efficiency in the medication reconciliation process. In daily practice these should be implemented to save costs and gain time for other interventions. Depending on the local situation the following efficiency improvements can be implemented:

1. Performing medication reconciliation in patients at low risk by healthcare professionals using electronic tools during routine care visits. There are a variety of electronic tools that have been developed to aid in the medication reconciliation process. [21] Already existing tools are being integrated in daily practice to reduce the daily workload of the medication reconciliation process of pharmacy technicians and other health care professionals. Patients at low risk of medication errors in transitions of care use less medication because number of medications is the most important risk factor of medication errors at transitions in care. Leaving the medication reconciliation in this patient group to other healthcare professionals during routine visits is possible due to the low number of medications and the low risk of medication errors. Preferably aided by an electronic system that integrates medication from multiple sources and makes it therefore very easy for the healthcare professional to identify the current medication use. However, when changing medication reconciliation procedures, the correct identification of low risk patients should be evaluated. Daily practice is always different from the performed studies and therefore evaluation of changed methods is very important.
2. Implementing patient portal medication reconciliation
   Most time can be saved by having the patient perform the medication reconciliation themselves. In the current world wide COVID-19 pandemic and the fast digitalization of healthcare, patient portal medication reconciliation is the most efficiency improving intervention at the same time reducing face-to-face contact. Patient portal medication reconciliation will always need a validation step by a healthcare professional. The ideal patient portal medication reconciliation tool integrates medication information from multiple sources including over the counter medication and can transfer this to different healthcare systems from hospitals, primary care healthcare professionals and long-term care healthcare institutions.

The above described improvements should be implemented in combination because the implementation of the combined interventions, makes the entire process of medication reconciliation much more efficient. After implementation, hospitals should evaluate for their own situation if the interventions are actually quality improving and time saving. These results of evaluation after implementation should be shared outside of the hospital so that together everyone can learn what interventions in which

settings work, and equally important what does not work or what barriers are involved in specific settings.

In the ideal world a patient centered digital environment is available in which all information about medication use including over the counter medication is available. The patient can give healthcare professionals access to the digital environment and all prescribers prescribe in this system which automatically keeps the information up-to-date. In emergency situations healthcare professionals are able to access the information on the current medication use. All improvements described above are unnecessary when this would be realized. However with the current privacy laws this ideal solution is not likely to be feasible in the near future.

IMPLICATIONS FOR FUTURE RESEARCH

Implementation studies into patient portal medication reconciliation are warranted to gain more insight into facilitators and barriers for patients to use patient portal medication reconciliation. Furthermore, optimizing the patient portal medication reconciliation by removing barriers should be part of these implementation studies. Also, different electronic tools to facilitate medication reconciliation should be studied and preferably be compared in head-to-head studies so that the most effective tools can be used. The time gained in implementing these efficiency improvement should be used to further optimise safe medication use for every patient.

Using time saved by efficiency measures to optimize the medication process

Medication reconciliation has proven to prevent medication transfer errors.[11] However, studies into preventing readmissions and adverse drug events showed that performing medication reconciliation is often not enough to prevent readmissions and adverse drug events.[26] A Cochrane clinical answer by Burch et al in 2019 confirms these findings. They conclude that medication reconciliation only reduces the number of people who have medication discrepancies but has little or no impact on mortality, rehospitalizations or adverse drug events.[27] Only when performing a multifaceted intervention including medication reconciliation but also a patient interview aimed at reducing drug related problems this is more effective.

In these interventions it is essential to not only involve healthcare professionals in the hospital but also primary care or long-term care healthcare professionals, as patients spend the most time at home or in a long-term care facility. Future research should focus on the effect of these interventions on mortality and medication related hospital (re)admissions.

Medication reconciliation is always the first step in multifaceted transitional care interventions, because in order to detect medication related problems it is necessary to know which medication is in use.[28] Combining all interventions described in this thesis

will minimize the time needed for this first step, which may facilitate implementation of the other interventions. This will ultimately lead to a safe patient journey.

REFERENCES

1. Cheema, E., et al., *The impact of pharmacists-led medicines reconciliation on healthcare outcomes in secondary care: A systematic review and meta-analysis of randomized controlled trials.* PLoS One, 2018. **13**(3): p. e0193510.
2. Mekonnen, A.B., et al., *Impact of electronic medication reconciliation interventions on medication discrepancies at hospital transitions: a systematic review and meta-analysis.* BMC Med Inform. Decis Mak, 2016. **16**: p. 112.
3. Hammad, E.A., et al., *Pharmacy led medicine reconciliation at hospital: A systematic review of effects and costs.* Res Social Adm Pharm, 2017. **13**(2): p. 300-312.
4. Meguerditchian, A.N., et al., *Medication reconciliation at admission and discharge: a time and motion study.* BMC Health Serv Res, 2013. **13**: p. 485.
5. Ebbens, M.M., et al., *Risk factors for medication errors at admission in preoperatively screened patients.* Pharmacoepidemiol Drug Saf, 2018. **27**(3): p. 272-278.
6. Ebbens, M.M., et al., *Prospective Validation of a Risk Prediction Model to Identify High-Risk Patients for Medication Errors at Hospital Admission.* Ann Pharmacother, 2018. **52**(12): p. 1211-1217.
7. Sessa, M., et al., *Artificial Intelligence in Pharmacoepidemiology: A Systematic Review. Part 1-Overview of Knowledge Discovery Techniques in Artificial Intelligence.* Front Pharmacol, 2020. **11**: p. 1028.
8. Golas, S.B., et al., *A machine learning model to predict the risk of 30-day readmissions in patients with heart failure: a retrospective analysis of electronic medical records data.* BMC Med Inform Decis Mak, 2018. **18**(1): p. 44.
9. Mahmoudi, E., et al., *Use of electronic medical records in development and validation of risk prediction models of hospital readmission: systematic review.* Bmj, 2020. **369**: p. m958.
10. Liu, Y., et al., *How to Read Articles That Use Machine Learning: Users' Guides to the Medical Literature.* Jama, 2019. **322**(18): p. 1806-1816.
11. Mekonnen, A.B., A.J. McLachlan, and J.A. Brien, *Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis.* J Clin Pharm Ther, 2016. **41**(2): p. 128-144.
12. Redmond, P., et al., *Impact of medication reconciliation for improving transitions of care.* Cochrane Database of Systematic Reviews, 2018(8).
13. Champion, H.M., J.A. Loosen, and K.A. Kennelty, *Pharmacy Students and Pharmacy Technicians in Medication Reconciliation: A Review of the Current Literature.* J Pharm Pract, 2019. **32**(2): p. 207-218.
14. Ebbens, M.M., et al., *Pre-operative medication reconciliation by pharmacy technicians or anaesthesiologists.* Eur J Anaesthesiol, 2021. **38 Suppl 1**: p. S71-s72.
15. Centraal Bureau voor de Statistiek. *Ziekenhuisopnamen en patiënten 2017*. 2017 [cited 2020 10 Nov].
16. Ebbens, M.M., et al., *Prevalence of medication transfer errors in nephrology patients and potential risk factors.* Eur J Intern Med, 2019. **70**: p. 50-53.
17. Horsky, J., E.A. Drucker, and H.Z. Ramelson, *Higher accuracy of complex medication reconciliation through improved design of electronic tools.* J Am Med Inform Assoc, 2018. **25**(5): p. 465-475.

18. Tamblyn, R., et al., *Improving patient safety and efficiency of medication reconciliation through the development and adoption of a computer-assisted tool with automated electronic integration of population-based community drug data: the RightRx project.* J Am Med Inform Assoc, 2018. **25**(5): p. 482-495.

19. Lesselroth, B.J., et al., *Evaluation of Multimedia Medication Reconciliation Software: A Randomized Controlled, Single-Blind Trial to Measure Diagnostic Accuracy for Discrepancy Detection.* Appl Clin Inform, 2018. **9**(2): p. 285-301.

20. Marien, S., et al., *A web application to involve patients in the medication reconciliation process: a user-centered usability and usefulness study.* J Am Med Inform Assoc, 2018. **25**(11): p. 1488-1500.

21. Wang, H.M., et al., *Electronic medication reconciliation in hospitals: a systematic review and meta-analysis.* European Journal of Hospital Pharmacy-Science and Practice, 2018. **25**(5): p. 245-250.

22. Ebbens, M.M., et al., *The Effect of Medication Reconciliation via a Patient Portal on Medication Discrepancies: A Randomized Noninferiority Study.* J Am Med Dir Assoc, 2021.

23. Kim, J.M., et al., *Evaluation of Patient and Family Engagement Strategies to Improve Medication Safety.* Patient, 2018. **11**(2): p. 193-206.

24. Klopotowska J., et al., *MijnDossier voor mijn medicatie - Herontwerp van medicatieverificatie met het patiëntenportaal* 2018, Amsterdam UMC, NFU, ZonMw: Amsterdam p. 92.

25. Nederlandse Vereniging van Ziekenhuizen., *Versnellingsprogramma Informatie-uitwisseling Patiënt en Professional (VIPP)*, VWS, Editor. 2021.

26. Guisado-Gil, A.B., et al., *Impact of medication reconciliation on health outcomes: An overview of systematic reviews.* Res Social Adm Pharm, 2020. **16**(8): p. 995-1002.

27. Burch, J. and U. Ronellenfitsch, *What are the effects of medication reconciliation for improving transitions of care?* Cochrane Clinical Answers, 2019.

28. Patel, E., J.M. Pevnick, and K.A. Kennelty, *Pharmacists and medication reconciliation: a review of recent literature.* Integr Pharm Res Pract, 2019. **8**: p. 39-45.

CHAPTER

10

ENGLISH SUMMARY

ENGLISH SUMMARY

Medication transfer errors are defined as unintentional discrepancies between medication used at home and medication prescribed at hospital admission, or between medication prescribed at discharge and medication used at home after discharge. These medication transfer errors can lead to patient harm and/or extended hospital admission. Medication transfer errors can be reduced by the process of medication reconciliation, in which multiple information sources are combined such as a medication overview from a community pharmacy or general practitioner, the hospital electronic patient record and information provided by a (semi)structured patient interview. Eventually medication reconciliation leads to the Best Possible Medication History (BPMH). The BPMH is subsequently compared to the current medication use and any discrepancies are resolved. It is known that the highest quality can be obtained when medication reconciliation is performed by pharmacy professionals. However, performing medication reconciliation in every transfer of care situation is very time consuming. Therefore this thesis focused on improving efficiency in medication reconciliation. Three ways to improve efficiency in medication reconciliation were studied in this thesis as described in the general introduction (**chapter 1**). First, risk factors of medication errors were explored in order to be able to perform medication reconciliation only in patients at high-risk of medication errors. Second, allocating patients to different methods of medication reconciliation based on risk factors was studied. Finally, patient portal medication reconciliation was investigated to establish non-inferiority to pharmacy-led medication reconciliation.

The first part of this thesis focuses on the identification of risk factors of medication transfer errors. In c**hapter 2** existing literature is systematically reviewed to assess independent risk factors of medication errors in transfers of care. After an extensive systematic literature search 44 studies on risk factors of medication errors at transitions of care were identified. The risk factor found in more than 90% of the studies at admission and more than 75% of the studies at discharge was number of medications in use. At admission age, type of medication, information sources for medication reconciliation, and comorbidity at admission were respectively the second to fifth most frequently identified risk factors. As risk factors of medication errors at discharge the rest of the top 5 consisted of physician level, medication changes during hospitalisation, hospital ward, and residential situation. In **chapter 3** risk factors of unintended medication discrepancies in patients admitted through the emergency department of a general hospital were studied. In a retrospective observational study results of medication reconciliation at admission were analysed to find medication discrepancies between the admission medication and the BPMH. Of 832 included patients 11.7% experienced at least one medication discrepancy. The number of pre-admission medications taken and age were both independently associated with the occurrence of a medication discrepancy. In c**hapter 4** risk factors of medication discrepancies in elective surgery patients of a general hospital were explored. At the preoperative screening (POS) elective surgery

medication reconciliation in every patient is performed to facilitate the anaesthesiologist in determining the medical condition and advising the patient on medication that needs to be discontinued before surgery. As the preoperative screening is planned between one day and three months before surgery, medication changes can take place between the POS and admission in the hospital. The aim of this study was to determine the proportion of preoperatively screened patients in which medication errors at admission were found, and to identify risk factors leading to these errors. Of the included 183 patients, 32.8% had at least one medication discrepancy. However, less than 10% of these discrepancies were rated as high risk. Number of medications and respiratory comorbidity were independently associated with the occurrence of medication errors at admission. From these risk factors a risk prediction model was constructed. **Chapter 5** described the validation study to assess if the risk prediction model that is built in **chapter 4** also applied to a different patient population. In a university hospital population, elective surgery patients who received medication reconciliation at the POS were included at admission. Medication reconciliation was performed and medication transfer errors at admission were the primary endpoint. Of the 368 included patients, 45% had at least one medication error at admission. The risk prediction model developed in **chapter 4** predicted only half of the patients with a medication error at admission correctly and was therefore not suitable to identify patients at high risk of medication errors at admission. The number of medications was the only common risk factor of medication errors at admission in both populations.

The second part of this thesis describes two studies of methods to perform medication reconciliation in a more efficient way. In **chapter 6** we studied if allocating low risk patients, with only one or none medications in use, to medication reconciliation by an anaesthesiologist during a routine visit was safe. In patients using two or more medications, medication reconciliation was performed by a pharmacy technician. The primary outcome was the proportion of patients with one or more medication errors at admission. Of the 367 included patients, in 201 medication reconciliation was performed by the pharmacy technician and in 166 by the anaesthesiologist. The percentage of patients with at least one medication error at admission was 44% and 47% respectively and did not differ significantly between the two groups. Therefore we conclude that allocating patients to an anaesthesiologist to perform medication reconciliation when using one or no medication is safe. **Chapter 7** describes a retrospective observational cohort study concerning medication reconciliation in an outpatient nephrology transplant population. Medication reconciliation was performed by a medical attendant using an electronic tool prior to an outpatient nephrologist visit. The electronic tool 'Medical Dashboard' aided the medication reconciliation process in integrating the medication use from the electronic hospital record and the dispensing information from the community pharmacy. This enabled the medical attendant to perform the medication reconciliation. The primary endpoint was the proportion of patients with at least one medication transfer error. As secondary outcomes risk factors of medication transfer errors, type and potential

harm of the medication errors and medication classes were investigated. Medication transfer errors were very common in this population, the medical attendant identified 61.8% of the patients having at least one medication transfer error. The number of medications was significantly associated with the occurrence of medication transfer errors.

The third part of this thesis describes patient participation in medication reconciliation using a patient portal. In chapter 8 a new strategy in medication reconciliation was studied. In an open randomized controlled non-inferiority trial patients of a university medical center were randomized in medication reconciliation using a patient portal and medication reconciliation by a pharmacy technician. The patient performed medication reconciliation using an application in which patients were presented with a medication list which they could assess and complete. The primary endpoint was the number of medication discrepancies compared to the community pharmacy dispensing data in the nationwide medication record system. Secondary, time investment and patient satisfaction were studied. In this study 499 patients were included, the mean number of medication discrepancies between the medication overview and the community pharmacy dispensing data was 2.6 ± 2.5 and 2.8 ± 2.7 for the patient portal medication reconciliation and pharmacy-led medication reconciliation respectively. This difference was not statistically significant and within the predefined non-inferiority margin. Medication reconciliation using the electronic tool saved on average 2.9 minutes per patient. Patients were generally satisfied with both medication reconciliation methods with an average of 8.1 and 8.7 in a ten point scale for the patient portal mediation reconciliation and pharmacy-led medication reconciliation, respectively. We concluded that medication reconciliation via a patient portal is non-inferior to medication reconciliation by a pharmacy technician and saved time in the medication reconciliation process. This time saving would increase to almost 7 minutes per patient in case of system optimalization (automatic transfer of medication information between patient portal and hospital medical record).

In chapter 9 the findings of the studies in this thesis are discussed. With regard to patients at high-risk of medication errors new methods need to be explored to create better predicting models possibly with the use of artificial intelligence. Allocating patients to different healthcare professionals to perform medication reconciliation seems possible based on chapter 6 and 7, however the quality of the medication reconciliation aided by electronic tools needs further exploration in future research. The concept that patients can be involved in their own medication reconciliation is proven in this thesis. However, future studies should investigate which patients are not able to generate a reliable medication overview and find alternatives for this group. Implementing electronic tools to facilitate medication reconciliation, performing medication reconciliation in patients at low risk by healthcare professionals during routine visits and patient portal medication reconciliation in daily practice will make medication reconciliation more efficient.

CHAPTER

11

NEDERLANDSE SAMENVATTING

NEDERLANDSE SAMENVATTING

Inleiding

Wanneer patiënten opgenomen worden in het ziekenhuis is het belangrijk om te weten welke medicijnen zij gebruiken. Het in kaart brengen van de medicijnen van een patiënt heet medicatieverificatie. Uit verschillende onderzoeken weten we dat medicatieverificatie fouten bij het voorschrijven van medicijnen kan voorkomen. Als een arts niet goed weet welke medicijnen een patiënt al heeft kan de arts zich vergissen. Hij kan dan medicijnen voorschrijven die een ongewenste wisselwerking hebben met de medicijnen die al gebruikt worden. Of hij kan medicijnen dubbel voorschrijven. Medicatieverificatie gebeurt door informatie uit verschillende bronnen te combineren. Die bronnen zijn bijvoorbeeld de aflevergegevens van de openbare apotheek en de gegevens in het ziekenhuissysteem. Vervolgens wordt de informatie besproken met de patiënt. Hieruit volgt een zogenaamd actueel medicijnen overzicht (AMO): een zo goed mogelijk overzicht van alle medicijnen die de patiënt gebruikt. We weten uit eerder onderzoek dat uitvoering van medicatieverificatie door apothekersassistenten leidt tot betrouwbaardere overzichten van de medicijnen dan wanneer dit door artsen of verpleegkundigen wordt gedaan. In de praktijk is het echter niet mogelijk om voor alle patiënten in het ziekenhuis medicatieverificatie door een apothekersassistent te laten uitvoeren, omdat daar simpelweg de mankracht voor ontbreekt. In dit proefschrift zijn we daarom op zoek gegaan naar manieren om het proces van medicatieverificatie zo efficiënt mogelijk in te richten. Het proefschrift is opgedeeld in drie delen. In deel 1 hebben we onderzocht welke patiënten een groter risico lopen op fouten in het medicijnen overzicht bij opname en ontslag uit het ziekenhuis en bij welke patiënten we dus medicatieverificatie moeten uitvoeren. In deel 2 hebben we gekeken naar manieren om de efficiëntie van medicatieverificatie te vergroten. Dit kan door bij patiënten met een laag risico andere zorgverleners (artsen of doktersassistenten) in te zetten, die de patiënt toch al spreken. In deel 3 hebben we onderzocht of de patiënt zelf een grotere rol kan spelen in de medicatieverificatie met behulp van een computerprogramma.

Het doel van dit proefschrift is:

» In kaart brengen welke patiënten een groter risico lopen op medicatiefouten die worden voorkomen door medicatieverificatie.

» Onderzoeken welke zorgprofessionals en hulpmiddelen we kunnen inzetten in plaats van apothekersassistenten.

» Nagaan of de patiënt zelf medicatieverificatie kan uitvoeren via de computer of een mobiel apparaat.

Hoog risico patiënten

In het eerste deel van dit proefschrift zijn verschillende onderzoeken uitgevoerd naar patiënten die een hoog risico lopen op medicatiefouten. In **hoofdstuk 2** hebben we gekeken wat de bestaande literatuur zegt over de risicofactoren voor medicatiefouten bij opname of ontslag uit het ziekenhuis. Voor zowel opname als ontslag hebben we een top 5 opgesteld van meest gevonden risicofactoren. Zowel bij opname als ontslag staat op nummer 1 het aantal medicijnen dat een patiënt gebruikt. Dat wil zeggen: Hoe meer medicijnen mensen gebruiken hoe hoger de kans op fouten. Bij opname wordt het aantal medicijnen gevolgd door hogere leeftijd, bepaalde soorten medicijnen die in gebruik zijn, informatiebronnen die zijn gebruikt voor medicatieverificatie en ziektes die de patiënt heeft. Bij ontslag wordt het aantal medicijnen gevolgd door opleidingsniveau van de arts (bijvoorbeeld basisarts of specialist), aantal wijzigingen in medicijnen tijdens opname, afdeling waar de patiënt opgenomen lag in het ziekenhuis, en hoe de patiënt woont (zelfstandig of in een instelling). In **hoofdstuk 3** hebben we op een spoedeisende hulp (SEH) gekeken welke risicofactoren er zijn voor medicatiefouten bij opname op de SEH. We zijn nagegaan welke verschillen er zijn tussen het actueel medicijnen overzicht na medicatieverificatie en de voorgeschreven medicijnen bij opname in het ziekenhuis. Van de 832 patiënten had 11,7% een medicatiefout bij opname. Het aantal medicijnen dat iemand gebruikt en de leeftijd verhoogden de kans op de aanwezigheid van een medicatiefout bij opname. In **hoofdstuk 4** hebben we gekeken welke risicofactoren voorkomen bij gepland opgenomen patiënten. Bij geplande opnames wordt de medicatieverificatie vaak uitgevoerd tijdens een zogenaamde preoperatieve screening (POS). Dit is een spreekuur bij de anesthesioloog, die dan bepaalt of de patiënt fit genoeg is om geopereerd te worden. Om dit te kunnen inschatten moet hij ook weten welke medicijnen de patiënt gebruikt. De POS gebeurt een aantal dagen tot weken voor de operatie. Uit ons onderzoek bleek dat bij een derde van de 183 patiënten er inmiddels bij opname medicijnen gewijzigd waren. De gewijzigde medicatie bij opname zou echter slechts in 10% van deze patiënten potentieel ernstige gevolgen kunnen hebben. De risicofactoren die hier zijn gevonden waren een groter aantal medicijnen in gebruik, het hebben van een cardiovasculaire aandoening en het hebben van astma/COPD. Met die risicofactoren hebben we een model gemaakt dat kan voorspellen welke patiënt het grootste risico loopt op medicatiefouten. In **hoofdstuk 5** hebben we in een ander ziekenhuis, bij hetzelfde type patiënten op de POS gekeken of dit model inderdaad een goede voorspelling van medicatiefouten maakt. In dit onderzoek werd bij 45% van de 368 patiënten een medicatiefout bij opname gevonden. Helaas bleek het model uit **hoofdstuk 4** niet voldoende voorspellende waarde te hebben. Het kan dus niet gebruikt worden om patiënten te verdelen in een groep waarbij de medicatieverificatie wel of niet herhaald moet worden. Het aantal medicijnen in gebruik was de enige risicofactor die overeenkwam in beide onderzoeken.

Efficiënter inrichten medicatieverificatie

In het tweede deel van dit proefschrift hebben we gekeken naar het inzetten van andere methoden om medicatieverificatie efficiënter te maken. In **hoofdstuk 6** hebben we de uitvoering van de medicatieverificatie door verschillende zorgverleners onderzocht. Op basis van de risicofactor 'aantal medicijnen' zijn deze bij een bepaalde zorgverlener ingedeeld. Tijdens de POS werd bij patiënten met één of geen medicijnen de medicatieverificatie door de anesthesioloog uitgevoerd tijdens het routine bezoek. De apothekersassistent deed de medicatieverificatie bij alle andere patiënten. Vervolgens hebben we de medicatiefouten bij opname in deze twee groepen vergeleken. Hieruit bleek dat het aantal patiënten met een medicatiefout bij opname, respectievelijk 44 en 47%, niet significant verschilde tussen de twee groepen. Daaruit concluderen we dat het laten uitvoeren van medicatieverificatie door een anesthesioloog tijdens een routine bezoek veilig kan voor patiënten met een laag risico. In **hoofdstuk 7** is de medicatieverificatie onderzocht bij niertransplantatie patiënten die voor een poliklinisch bezoek bij de nefroloog komen. Voor dit bezoek heeft een doktersassistent medicatieverificatie uitgevoerd met behulp van het computerprogramma: 'Medical Dashboard'. Dit programma combineert de gegevens van de medicijnen zoals afgeleverd door de openbare apotheek met de medicatiegegevens uit het ziekenhuissysteem en geeft dit overzichtelijk weer met de reden voor gebruik. De doktersassistent neemt vervolgens deze lijst door met de patiënt. Zo ontstaat een overzicht van de gebruikte medicijnen. Als de patiënt het zelf niet goed weet, geeft de doktersassistent aan dat de arts er nog naar moet kijken. Op deze manier kon de doktersassistent bij twee derde van de patiënten medicatiefouten voorkomen. Het aantal medicijnen in gebruik was wederom een risicofactor voor medicatiefouten.

Medicatieverificatie door de patiënt

In het derde deel van dit proefschrift zijn we nagegaan of patiënten zelf hun eigen medicatieverificatie kunnen uitvoeren met behulp van een computerprogramma. In **hoofdstuk 8** is een onderzoek beschreven waarbij patiënten zijn verdeeld in twee groepen. De eerste groep heeft vanuit huis de eigen medicatieverificatie uitgevoerd met een computerprogramma genaamd 'Zorgdoc'. Hierbij maakten patiënten gebruik van een computer, of van een mobiel apparaat (telefoon of tablet). Bij de tweede groep heeft de apothekersassistent de medicatieverificatie uitgevoerd in het ziekenhuis. De indeling in deze groepen is door middel van loting gebeurd. Vervolgens zijn we voor beide groepen nagegaan bij hoeveel medicijnen het actueel medicatie overzicht na medicatieverificatie verschilde van het overzicht van de openbare apotheek. In dit onderzoek hebben 499 patiënten meegedaan. Het gemiddeld aantal verschillen tussen het actueel medicatieoverzicht na medicatieverificatie en het overzicht van de openbare apotheek was 2,6 voor patiënten die zelf de medicatieverificatie deden en 2,8 voor patiënten waarbij de apothekersassistent dit deed. Het verschil hiertussen is niet

significant. Bij medicatieverificatie door de patiënt zelf werd gemiddeld 3 minuten per patiënt bespaard. Deze tijdsbesparing zou verhoogd kunnen worden naar bijna 7 minuten als het computerprogramma gekoppeld zou zijn met het ziekenhuissysteem. Patiënten waren tevreden over beide vormen van medicatieverificatie. Ze gaven gemiddeld een 8,1 voor het computerprogramma en een 8,7 voor de apothekersassistent, op een schaal van 1 tot 10. Uit dit onderzoek concluderen we dat patiënten goed in staat zijn zelf hun medicatieverificatie uit te voeren en dat dit tijd kan besparen voor apothekersassistenten.

Beschouwing

In **hoofdstuk 9** worden alle beschreven onderzoeken beschouwd en vergeleken met nieuwe literatuur. Met betrekking tot de patiënten met een hoog risico op medicatiefouten hebben we laten zien dat het niet eenvoudig is om een goed risicomodel te maken. Aanbevolen wordt om in de toekomst andere methoden te gebruiken om patiënten met een hoog risico te onderscheiden. Dit zou bijvoorbeeld kunnen met de hulp van kunstmatige intelligentie. Daarmee kunnen wellicht risicofactoren gevonden worden, die nu nog onbekend zijn.

In het tweede deel van het proefschrift hebben we gezien dat andere zorgverleners (al dan niet met behulp van een computerprogramma) die medicatieverificatie kunnen uitvoeren. Onderzoeken waarbij patiënten via loting over een groep 'andere zorgprofessional' en een groep 'apothekersassistent' worden verdeeld moeten nu opgezet worden. Dit is nodig om definitief te bewijzen dat medicatieverificatie door die andere zorgprofessional net zo goed is als de huidige gouden standaard door een apothekersassistent. In **hoofdstuk 8** van dit proefschrift hebben we aangetoond dat patiënten hun eigen medicatieverificatie kunnen uitvoeren met behulp van de computer. Echter, verder onderzoek is nodig naar welke patiënten dit zelf kunnen. Voor de patiëntengroep die dit niet (volledig) zelfstandig kan, moet gezocht worden naar welke alternatieven hiervoor wel werken. Uiteindelijk kan het gebruik van computerprogramma's en het laten uitvoeren van medicatieverificatie door andere zorgverleners tijdens routine bezoeken het proces van medicatieverificatie efficiënter maken.

A

APPENDICES

CURRICULUM VITAE

Marieke Marjet Ebbens-de Jong was born on May 4th, 1988 in Utrecht. After she completed her secondary school (VWO) at the Montessori Lyceum Herman Jordan in Zeist, she started to study Pharmacy at Utrecht University. During her Master study she followed a research internship at GGz Centraal entitled 'Diabetes Mellitus in Psychiatric Illness, effect of drug, disease or both?'. She obtained her Master's degree in 2012.

In September 2012, Marieke started her professional career at the department of Hospital Pharmacy of the Erasmus Medical Center in Rotterdam. In June 2013 she started at the Zaans Medical Center in Zaandam in the policlinic pharmacy, in November 2013 Marieke started her hospital pharmacy residency there. In 2015 she was president of the Association of Physicians in Training in the Zaans Medical Center. Marieke continued her hospital pharmacy residency in January 2016 in the Leiden University Medical Center in Leiden. In 2015 Marieke started to combine the hospital pharmacy training with a PhD research project at the Erasmus University Medical Center in Rotterdam, supervised by prof. dr. P.M.L.A. van den Bemt.

In 2017 Marieke finished her hospital pharmacy residency and started working as a hospital pharmacist at St Jansdal Hospital in Harderwijk, the Netherlands. In 2020 she finished the masterclass 'Behandelaarschap' organized by the Dutch Association of Hospital Pharmacists.

Marieke lives in Amersfoort together with Berry and their son Simon.

LIST OF PUBLICATIONS

Publications (this thesis)

Ebbens MM, Gombert-Handoko KB, Al-Dulaimy M, van den Bemt PMLA, Wesselink EJ. Risk factors for medication errors at admission in preoperatively screened patients. *Pharmacoepidemiol Drug Saf*. 2018 Mar;27(3):272-278. doi: 10.1002/pds.4380.

Ebbens MM, Laar SAV, Wesselink EJ, Gombert-Handoko KB, van den Bemt PMLA. Prospective Validation of a Risk Prediction Model to Identify High-Risk Patients for Medication Errors at Hospital Admission. *Ann Pharmacother*. 2018 Dec;52(12):1211-1217. doi: 10.1177/1060028018784905

Van Der Luit CD, De Jong IR, **Ebbens MM**, Euser S, Verweij SL, Van Den Bemt PM, Luttikhuis HM, Becker ML. Frequency of occurrence of medication discrepancies and associated risk factors in cases of acute hospital admission. *Pharm Pract (Granada)*. 2018 Oct-Dec;16(4):1301. doi: 10.18549/PharmPract.2018.04.1301.

Ebbens MM, Errami H, Moes DJAR, van den Bemt PMLA, van der Boog PJM, Gombert-Handoko KB. Prevalence of medication transfer errors in nephrology patients and potential risk factors. *Eur J Intern Med*. 2019 Dec;70:50-53. doi: 10.1016/j.ejim.2019.09.003.

Ebbens MM, van Dorp ELA, Gombert-Handoko KB, van den Bemt PMLA. Medication Reconciliation at the Preoperative Screening by Pharmacy Technicians Compared to Anaesthesiologists. *Eur J Anaesthesiol*. 2021 Mar;38:S71-72. doi: 10.1097/EJA.0000000000001390

Ebbens MM, Gombert-Handoko KB, Wesselink EJ, van den Bemt PMLA The effect of medication reconciliation via a patient portal on medication discrepancies; a randomized non-inferiority study. J Am Med Dir Assoc. 2021 Apr 24;S1525-8610(21)00318-2. doi: 10.1016/j.jamda.2021.03.022.

In preparation (this thesis)

Ebbens MM, Laar SAV, Wesselink EJ, Gombert-Handoko KB, van den Bemt PMLA. Systematic review of risk factors of medication errors in transitions of care. Manuscript in preparation.

Other publications

Ebbens MM, Verster JC. Clinical evaluation of zaleplon in the treatment of insomnia. *Nat Sci Sleep*. 2010 Jul 20;2:115-26. doi: 10.2147/nss.s6853.

Vinkers CH, Penning R, **Ebbens MM**, Hellhammer J, Verster JC, Kalkman CJ and Olivier B. Stress-Induced Hyperthermia in Translational Stress Research. *The Open Pharmacology Journal*. 2010, 4, 30-35. doi: 1874-1436/10.

Ebbens MM, Bouwman N, Wesselink EJ. Medicatieverificatie bij geplande opnames, is het medicatieoverzicht bij opname compleet? *Nederlands Platform voor Farmaceutisch Onderzoek*. 2016;1:a1620.

Ebbens MM, Gombert-Handoko KB, Al-Dulaimy M, van den Bemt PMLA, Wesselink EJ Risicofactoren voor medicatiefouten na eerdere medicatieverificatie bij electieve opnames. *Nederlands Platform voor Farmaceutisch Onderzoek*. 2018;3:a1661

Smeets DLM, Gombert-Handoko KB, **Ebbens MM**. Preoperatieve medicatieverificatie bij electieve opnames in Nederlandse ziekenhuizen. *Nederlands Platform voor Farmaceutisch Onderzoek*. 2020;5:a1728

DANKWOORD

Er zijn heel veel mensen die hebben bijgedragen aan het tot stand komen van dit proefschrift. In dit dankwoord wil ik van de gelegenheid gebruik maken om deze mensen te bedanken.

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Simon, jouw komst zorgde voor een harde deadline om dit proefschrift af te ronden. Mijn onderzoeksdag wordt nu mijn mamadag, ik kijk ontzettend uit naar alle avonturen die wij samen gaan beleven.

PHD PORTFOLIO

Name PhD student: **M.M. Ebbens**
Erasmus MC Department: Hospital Pharmacy
PhD period: 4/2016 – 5/2021
Promotor: Prof dr. P.M.L.A. van den Bemt
Co-promotor: dr. K.B. Gombert-Handoko
Supervisor: E.J. Wesselink

	Year	ECTS
General courses		
CORAZ (Onderzoeksdag 1 en 2)	2015	1
VAZA time management	2015	0.3
BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2016	1.5
OpenClinica	2016	0.3
Klinische onderwijskunde	2016	0.3
Biomedical English Writing	2017	2
Research Integrity	2017	0.3
Biostatistics	2017	2
Update BROK	2020	0.3
Presentations		
Zaans Medisch Centrum Wetenschapsdag. Oral presentation	2014	0.5
Longfonds patiëntenbijeenkomst. Oral presentation	2015	1
Referaat regiobijneekomst VUmc. Oral presentation	2015	0.5
Research meeting LUMC. Oral presentation	2016	0.5
Presentation at PRISMA symposium	2017	0.5
Research meeting LUMC. Oral presentation	2017	0.5
Presentations at NVZA congress	2017	0.5
Poster ISPE congress	2018	0.3
Presentation pizza and science meeting LUMC	2018	0.5
Presentations at PRISMA symposium	2019	0.5
Poster ESRA congress	2019	0.3
Presentation at PRISMA symposium	2021	0.3
(Inter)national conferences		
Ziekenhuisfarmaciedagen, inchecken voor innovatie, Rotterdam	2016	0.3
Ziekenhuisfarmaciedagen, Bunnik	2017	0.3
PRISMA symposium	2017	0.3
PRISMA symposium	2018	0.3
ISPE congress	2018	0.6
EAHP congress	2019	0.9
PRISMA symposium	2019	0.3
ESRA congress	2019	0.6
PRISMA symposium	2021	0.3
Teaching		
Farmacokinetiek voor co-assistenten	2014-2015	0.5

PhD Portfolio (continued)

	Year	ECTS
Onderwijs dermatica voor co-assistenten	2016-2017	0.5
Werkcollege dermatica voor studenten farmacie	2016	0.3
Hoorcollege, werkcollege en practica rectale toedieningen	2016	1
Klinsche les acute opname afdeling over medicatie	2017	0.3
Introductiecollege Ziekenhuisfarmacie voor studenten farmacie	2017	0.2
Klinische les SEH over medicatie	2017	0.3
Supervising research projects		
Bachelors thesis (10 weeks)		
N. Saad (Utrecht University) "Risk factors for medication errors at admission in preoperatively screened patients: an observational cross sectional study"	2015	1
H. Hoogeveen (Leiden University) "Prevalence of remaining medication error types in different ATC groups after previous medicaiton reconciliation"	2017	1
B. Verdiesen (Leiden University) "Prevalence of cardiovascular agents, sedatives and analgesics in type and frequency of medication errors at admission"	2017	1
Master thesis (20-24 weeks)		
S. van Laar (Utrecht University) "Predicting high risk patients for medication errors at admission after earlier pharmacy-led medication reconciliation: a prospective validation study"	2016	2
H. Errami (Utrecht University) "Risk factors for medication discrepancies in nephrology outpatients"	2018	2
A. Akka (Leiden University) "Medication reconciliation using e-health"	2018	2
S. Appelman (Utrecht University) "Medication reconciliation using an ehealth application"	2019	2
A. Harrachi (Utrecht University) "Medication reconciliation using e-health tool: effect on time investment and medication errors."	2019	2
Other internships (5 weeks)		
D. Smeets (Utrecht University) "Preoperatieve medicatieverificatie bij electieve opnames in Nederlandse ziekenhuizen"	2019	0,5
Other		
Organizing multidisciplinary symposium 'Elektrolytes, refeeding en volume resuscitation'	2015	1
Organizing symposium 'Coach, cure and care'	2015	1
Organizing Coaching meeting 'werkdruk'	2016	1