Medication changes in patients transitioning between health care settings

Rutger Stuffken

The work in this thesis was performed at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences (Faculty of Science, Utrecht University), in collaboration with the Department of Clinical Pharmacy of Tergooiziekenhuizen Blaricum/Hilversum and the Department of Clinical Pharmacy of the University Medical Centre Utrecht.

Parts of this thesis were performed in collaboration with the following institutes:

* Outpatient Pharmacy Tergooiziekenhuizen Hilversum.
* Medical Centre Alkmaar, department of geriatric medicine.
* University of Applied Science Utrecht, Faculty Chair for Chronically Ill.

ISBN/EAN: 978-90-9026332-8

Cover and figure design: Rutger Stuffken
Figure editing and lay out: Elsbeth Kool, Kooldesign, Utrecht
Photography: Rutger Stuffken

Medication changes in patients transitioning between health care settings

Veranderingen in medicatie bij transities in de zorg

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G. J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
woensdag 23 november 2011 des middags te 2.30 uur

door
Rutger Stuffken

geboren op 11 augustus 1947

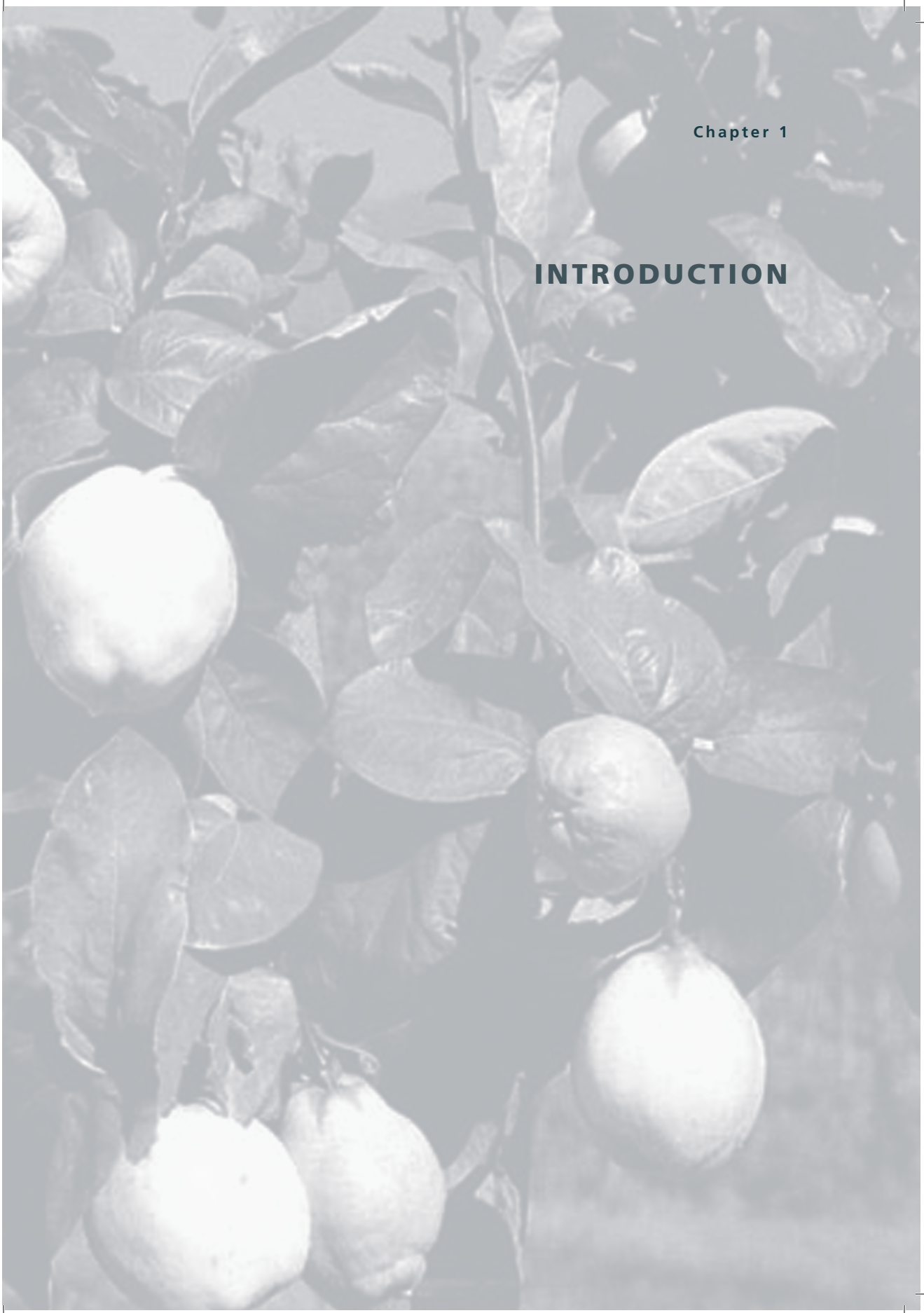
te Heerlen

Promotor: Prof.dr. A.C.G. Egberts

Co-promotor: Dr. E.R. Heerdink

Dit proefschrift werd mede mogelijk gemaakt met financiële steun van Tergooiziekenhuizen.

Contents



Chapter 1

INTRODUCTION

Medication changes in patients transitioning between health care settings

Medical errors and the harm that can result from these have received renewed and increasing attention throughout the world during the last decade. In 1999, the Institute of Medicine published its report "To Err is Human"[1], later followed by similar publications from other countries, like the UK and the Netherlands, which highlighted the magnitude of the problem of patients being largely unnecessarily harmed as the result of received medical care.[2-4] Medication is one of the most commonly applied medical interventions, and therapeutic progress has contributed significantly to the increase in life expectancy and quality of life. Despite the benefits of the progress in medical and pharmaceutical care, many medical and pharmacological decisions still carry the potential for iatrogenic harm.[5,6] Not all adverse events resulting from medical management are preventable, and unintended harm may be caused by non-preventable adverse effects of medical care. 'Primum non nocere' (first do no harm) is an often quoted term from Hippocrates. This phrase reminds health-care providers that they must consider the possible harm that any intervention might have and that for the individual patient, the treatment goal is an optimal balance between benefit and risk.

Errors in medical care can occur in all stages in the process of care (from diagnosis, to treatment, to preventive care) and in every health-care setting (e.g., homes, nursing homes, hospitals).[7] Although many of the available studies have focused on the hospital setting, medical errors present a problem in any setting, not just in hospitals. Medication errors are one of the most common types of medical error.[8] Medication errors may or more usually, may not result in harm to the patient. It has been estimated that 1%–2% of all patients admitted to the hospital suffer harm as a result of medication errors.[9] Other multicenter studies have identified the frequency of medication-related hospital admissions as falling in the range of 2.4% to 17%.[11,12] Leendertse *et al* analysed ninety-five studies with a range of reported prevalence of medication-related hospitalisations from 0.1% to 54%.[10] The Dutch HARM study showed that in the Netherlands, 5.6% of acute hospital admissions and 2.4% of all hospital admissions are due to medication; of these, almost half were considered potentially preventable.[2]

Continuity of care

Van Geffen suggested the use of 3 separate phases within the course of drug taking.[13] The course of drug taking can be described as a sequence of actions and is visualised in Figure 1.

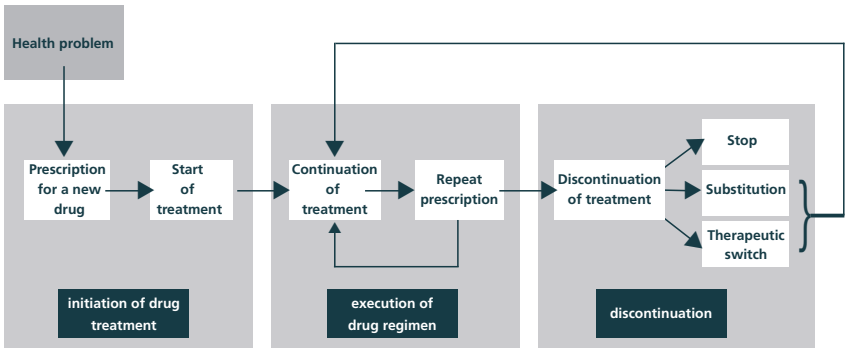


Figure 1. The sequence begins with a health problem and the prescribing of a drug for treatment of the disease. The sequence ends with the discontinuation of drug use. Discontinuation occurs when there is a therapeutic switch or when the drug is stopped, substituted by a branded or generic medicine or replaced with a drug with the same active substance but with a different strength and/or dosage form. An important proportion of drug-related problems occur when patients transition from one health-care setting to another setting. A transfer between care settings is associated with relevant changes in patient care and a transfer of responsibility. The separation of health care in the primary and secondary sectors is a risk factor for the lack of continuity of medical care and accounts for the discontinuities in pharmacotherapy [14-17]. As illustrated in Figure 2, prescribing drugs across health-care settings is quite complicated; multiple physicians are involved at different time-points.

When a transfer occurs between health-care settings or relocation to primary or secondary care occurs, a natural part of a patient's treatment is the evaluation of former drug treatments and of further indications for treatment. Patients are asked to continue prescribed medication, to discontinue medication, to switch to another brand or generic drug, to switch to a new dosage schedule, or to begin a new treatment.[18-21]

The following are intentional reasons for changing drug use: changes in a patient's clinical condition; determination that the prescribed agent was unnecessary, ineffective, contributing to toxicity or causing adverse reactions; or lack of availability of the prescribed drug in the local hospital's formulary.

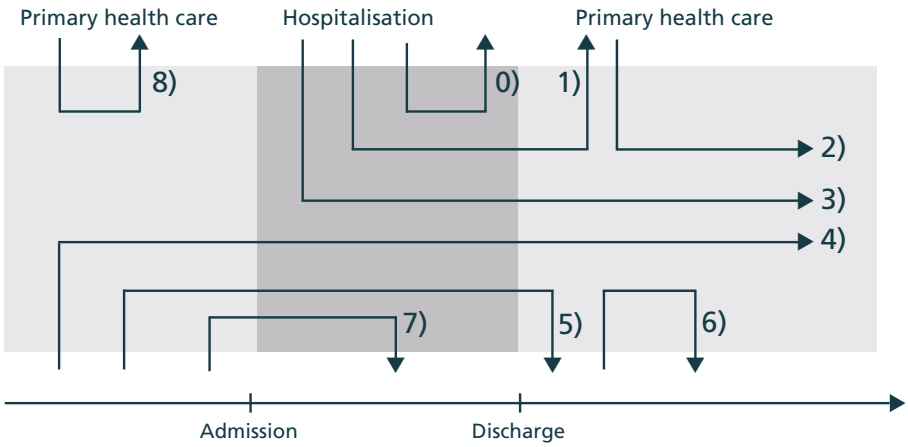


Figure 2. Patterns of drug use across health-care settings. Prescriptions are defined as medication only available by prescription as opposed to over-the-counter products. Drug use can be subdivided into the following categories: 0) Drugs prescribed during hospitalisation and stopped during hospitalisation. 1) Drugs prescribed during hospitalisation and used at discharge but stopped within a few weeks after discharge. 2) Drugs prescribed after discharge. 3) Drugs prescribed during hospitalisation and used after discharge. 4) Drugs prescribed before hospitalisation and used after discharge 5) Drugs prescribed before hospitalisation and discontinued after discharge. 6) Drugs prescribed after discharge and discontinued within a few weeks. 7) Drugs prescribed before hospitalisation and discontinued during hospitalisation. 8) Drugs prescribed before hospitalisation and discontinued before hospitalisation.

The discontinuation of drug use can also be unintentional. Unintentional changes in drug therapy imply that the physician is unaware of these changes. Unintentional changes occur most often at points of transition in care and can be the result of a lack of documentation and communication or may be due to hospital physicians forgetting to restart temporarily discontinued medications. [22–25] Discontinuation symptoms can cause significant morbidity, have adverse effects on patients' quality of life and may result in represcription of the withdrawn medications or in unnecessary renewed drug use.[26–28] Another aspect of safe drug use is the documentation of the use of non-prescription drugs. With transfers across health-care settings, adverse events related to drug use may also occur when there is no complete and up-to-date documentation available about the use of non-prescription drugs.

Several studies have explored medication therapy discontinuities at hospital admission or discharge. Most studies included a relatively low number of patients from one ward or one hospital and focused on changes in drug regimens either at admission or discharge.

Objective

The overall aim of this thesis is to determine the magnitude and outcome of the problem of medication changes associated with patients' transitioning between health-care settings. Another aim is to identify the determinants of these changes and which patients are at risk.

Outline

This thesis consists of 4 parts. In this introductory chapter (**Chapter 1**), the scope, objective and outline are described. Next, the individual research projects of this thesis are addressed in two chapters. **Chapter 2** focuses on hospitalisation as a determinant of medication changes. In Chapter 2.1, the association between discontinuities in medication used in a community setting and hospitalisation is described. The nature and frequency of discontinuities in drug treatment in a cohort of patients admitted and discharged from the hospital is described in Chapter 2.2. The association between discontinuities in the use of psychotropic drugs used in a community setting and hospitalisation is evaluated in Chapter 2.3. In Chapter 2.4, the impact of hospitalisation on prescribing and the long-term use of benzodiazepines in ambulatory care during the pre-hospitalisation and post-hospitalisation periods are investigated.

Chapter 3 focuses on medication changes as a determinant of hospitalisation. Assuming that the number of prescription changes is associated with hospitalisation, the difference in use and ability between prescription change intensity and chronic disease score was investigated (Chapter 3.1). In Chapter 3.2, we compare 6 different instruments for the assessment of anticholinergic (ACH) drug load. For each instrument, the strength of the association between the aggregate ACH drug load and the occurrence of delirium was calculated in a cohort of elderly patients admitted for orthopaedic surgery.

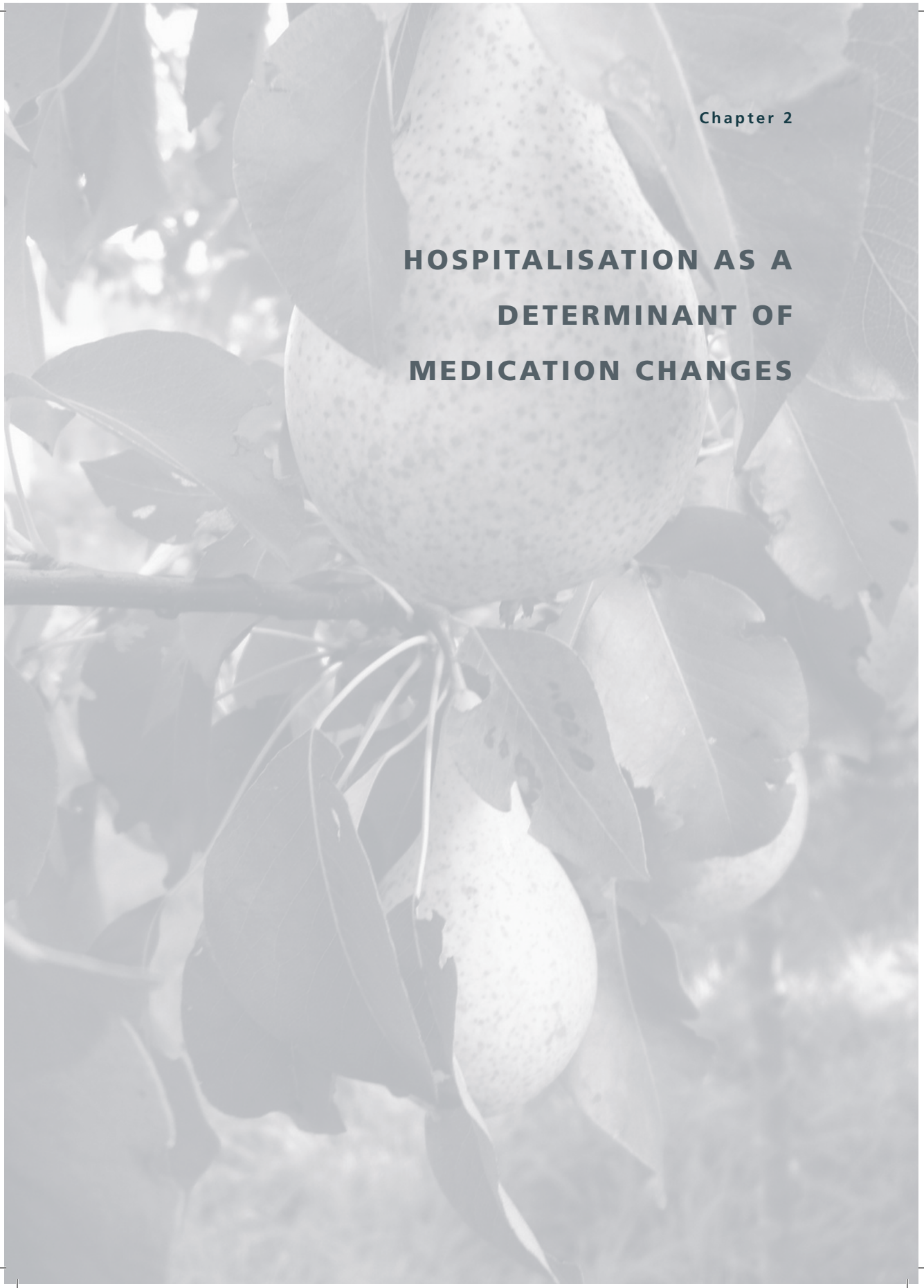
Finally, in **Chapter 4,** the results of these studies are discussed in a broader context, along with some future perspectives. Recommendations for physicians and pharmacists to improve care for patients are provided.

References

1. Institute of Medicine. To err is human: building a safer health system. Washington DC: National Academy Press, 1999
2. Leendertse AJ, Egberts ACG, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008;170;1890-6
3. Zegers M, de Bruijne MC, Wagner C, Groenewegen PP, Waaijman R, van der Wal G. Design of a retrospective patient record study on the occurence of adverse events among patients in Dutch hospitals. BMC Health Services Research 2007;7:27-38
4. Zegers M, de Bruijne MC, Wagner C, Hoornhout LHF, Waaijman R, Smits M, Hout FAG, Zwaan L, Christiaans-Dingelhoff I, Timmermans DRM, Groenewegen PP, van der Wal G. Adverse events and potentially preventable deaths in Duch hospitals: results of a retrospective patient record review study. Qual Saf Health Care 2009;18:297-302
5. Krishnan NR, Kasthuri BAS Iatrogenic disorders. Med J Armed Forces India 2005;61:2-6
6. Steel K, Gertman PM, Crescenzi C. Iatrogenic illness on a general medical serve at a university hospital. Qual Saf Health Care 2004;13:76-80
7. Vira T, Colquhoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. Qual Saf Health Care 2006;15:122-6
8. Leape LL, Brennan TA, Laird N, Lawthers AG *et al*. The nature of adverse events in hospitalised patients. Results of the Harvard medical practice study II. New England Journal of Medicine 1991;324:377-384
9. Barber ND, Dean BS. The incidence of medication errors and ways to reduce them. Clin Risk 1998;4;103-6
10. Leendertse AJ, Visser D, Egberts TCG, Van den Bemt PMLA The relationship between study characteristics and prevalence of medication-related hospitalisations: a literature review and novel analysis. Drug safety 2010;33:233-44
11. Onder G, Pedone C, Landi F, *et al* Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA), J Am Geriatr Soc. 2002;50:1962-8
12. Schneeweiss S, Hasford J, Göttler M, Hoffmann A, Riethling AK, Avorn J. Admission caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. Eur J Clin Pharmacol. 2002;58:285-291
13. Van Geffen ECG. Initiation, execution and discontinuation of antidepressant therapy [dissertation]. Utrecht: Utrecht University; 2008

14. Harder S, Fischer P, Krause-Schäfer M, Ostermann K, Helms G, Prinz H, Hahmann M, Baas H. Structure and markers of appropriateness, quality and performance of drug treatment over an 1-year period after hospital discharge in a cohort of elderly patients with cardiovascular diseases from Germany. Eur J Clin Pharmacol 2005; 60:797-805
15. Himmel W, Tabache M, Kochen MM. What happens to long-term medication when general practice patients are referred to hospital. Eur J Clin Pharmacol 1996;50:253-7
16. Himmel W, Kochen MM, Sorns U, Hummers-Pradier E. Drug changes at the interface between primary and secondary care. Int J Clin Pharmacol 2004;42:103-9
17. Omori DM, Potyk RP, Kroenke K. The adverse effects of hospitalisation on drug regimens. Arch Intern Med. 1991;151(8):1562-4
18. Beers MH, Dang J, Hasegawa J, Tamai IY. Influence of hospitalisation on drug therapy in the elderly. J Am Geriatr. Soc 1989;37:679-83
19. Laroche ML, Charmes JP, Nouaille Y, 4rier A, Merle L. Impact of hospitalisation in an acute geriatric unit on potentially inappropriate medication use. Drugs Aging 2006;23(1):49-59
20. Cornish PL, Knowles SR, Marchesano R, *et al.* Unintended medication discrepancies at the time of hospital admission. Arch Intern Med 2005;165:424-9
21. Vira T, Colquhoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. Qual Saf Health Care 2006;15:122-6.
22. Grimes TC, Duggan CA, Delaney TP, Graham IM, Conlon KC at all. Medication details documented on hospital discharge: cross-sectional observational study of factors associated with medication non-reconciliation. Br J Clin Pharmacol 71;2011:449-57
23. Witherington EMA, Pizada OM, Avery AJ. Communication gaps and readmissions to hospital for patients aged 75 years and older: observational study. Qual Saf Health Care 2008;17:71-5
24. Coleman EEA, Smith JD, Raha D, Min S-J. Post hospital medication discrepancies, prevalence and contributing factors. Arch Intern Med 2005;165:1842-7
25. Boockvar K, Fishman E, Kyriacou CK, Monias A, Gavi S, Cortes T. Adverse events due to discontinuation in drug use and dose changes in patients transferred between acute and long-term care facilities. Arch Intern Med 2004;164:545-50
26. Van der Linden MJ, Kerskes MCH, Bijl AMH, Maas HAAM, Egberts ACG, Jansen PAF. Represcription after adverse drug reaction in the elderly: a descriptive study. Arch. Intern Med 2006; 166(15):1666-7
27. Van der Linden MJ, Jansen PAF, van Geerenstein EV, van Marum RJ, Grouls RJE, Egberts ACG, Korsten EHM. Reasons for discontinuation of medication during hospitalisation and documentation thereof: a descriptive study of 400 geriatric and internal medicine patients. Arch. Intern Med 2010; 170(12):1085-7

28. Lejoyeux M, Adès J. Antidepressants discontinuation: a review of the literature. J Clin Psychiatry 1997;58(suppl 7):11-6



Chapter 2

HOSPITALISATION AS A DETERMINANT OF MEDICATION CHANGES

Chapter 2.1

THE ASSOCIATION BETWEEN HOSPITALISATION AND DISCONTINUITY OF MEDICATION THERAPY USED IN THE COMMUNITY SETTING IN THE NETHERLANDS

Rutger Stuffken
Eibert R. Heerdink
Fred H.P. de Koning
Patrick C. Souverein
Antoine C.G. Egberts

Ann Pharmacother 2008;42(7):933-9

Abstract

Background

Transitions from one healthcare setting to another often parallel transitions in health status and can be associated with intentional as well as unintentional changes in patient care. Hospitalisation may put patients at increased risk of discontinuity of medication use.

Objective

To assess the association between hospitalisation and medication therapy discontinuities.

Methods

A retrospective follow-up study was conducted, using data obtained from the PHARMO Record Linkage System. We randomly selected patients who had been hospitalised (index date) between July 1, 1998 and June 30, 2000. For each hospitalised patient, one non-hospitalised patient was matched on age, sex and geographic area and assigned the same index date as the corresponding hospitalised patient. The primary study outcome was the incidence of one or more medication therapy discontinuities at the index date and on several control moments during a period of 18 months before and 18 months after hospital admission. We defined 4 mutually exclusive types of discontinuities: generic/brand substitution, product substitution, therapeutic switch and stop.

Results

The study population comprised 8,681 hospitalised patients and an equal number of age/sex matched non-hospitalised patients. Of all hospitalised patients on drug therapy at the index date (n= 5,265) 3,322 patients (63.1%) had one or more medication therapy discontinuities at the index date compared to 1,390 patients (33.5%) of the non-hospitalised group taking medication at the index date (n=4,147). [RR 1.82 (95% CI 1.71-1.94)].

The highest risk estimate was found for therapeutic switch [RR 5.34 (95%CI 3.93-7.26)], followed by product substitution [RR 2.32 (95%CI 1.88-2.86)] and stop [RR 1.98 (95%CI 1.85-2.13)]. There was no increased risk for generic/brand name substitution [RR 0.87 (95%CI 0.72-1.06)].

Conclusions

Hospitalisation is associated with discontinuity of drugs used in the community setting. Medication stops were observed most frequently. Hospital safety programs should focus attention on medication therapy discontinuities at times of transition to ensure continuity of care in relation to drug therapy.

Introduction

Hospitalisation may put patients at increased risk of discontinuity of medication use.[1] Transitions from one healthcare setting to another often parallel transitions in health status and can be associated with intentional as well as unintentional changes in patient care.[2] Continuity of care (seamless care) in relation to medication management has been recognized as an important mechanism for further optimization of drug-related outcomes.[3] Medication errors related to transitions across care settings are common and receive a great amount of attention in the professional and lay press.[4,5] On the day of hospital admission, many of the prescribed drugs reflect the pre-admission pharmacotherapy initiated, by primarily general practitioners.[6,7] The reason for admission as well as changes in a patient's clinical condition will lead to changes in the drug therapy regimen: *i.e.* intentional discontinuities. Drugs may be added, switched, stopped or the dosages may be changed.[8-9] Differences in local drug formularies may also lead to intentional discontinuities. Unintentional changes in drug use after hospital admission or discharge are often the result of sub-optimal communication or information about prescribed drugs and differences in local formularies; these unintentional changes may jeopardize patient safety.[10-14] Unintentional changes in drug therapy imply that the physician is unaware of the changes. Several studies have explored medication therapy discontinuities at hospital admission or discharge. Most studies included a relatively low number of patients from one ward or one hospital, and are focussed on changes in drug regimes either at admission or at discharge. We conducted a longitudinal study in a large group of patients over 36 months using an extensive database. Our objective was to analyse the association between discontinuities in medication therapy used in the community setting and hospitalisations.

Methods

Setting

The setting of this study was the PHARMO Record Linkage System (RLS). (www.pharmo.nl). The PHARMO RLS includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all 950,000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 onwards.[15] In brief, the computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, physician, amount dispensed and prescribed dosage regimen. Drugs are coded according

to the Anatomical Therapeutic Chemical (ATC) classification system. Patient information includes sex and date of birth. Each patient is registered with an anonymous unique patient identification code that allows for observation of a patients drug therapy over time. The database does not provide information concerning the indication for use of the medicines or the complete registration of non-prescription medicines as indiviudels may also purchase these drugs from non-pharmacy outlets.
The hospital discharge records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge.

Study population

A retrospective follow-up study was conducted. Initially 10,000 patients who had been hospitalised between July 1,1998 and June 30, 2000 were randomly selected from the PHARMO RLS. The date of admission was termed the index date. For each hospitalised patient one non-hospitalised patient, matched on age, sex, and geographic area, was assigned the same index date as that of the corresponding hospitalised patient. Patients were included in this study only if medication data for the time window of 24 months before and 24 months after the index date were available.

Outcome

The primary study outcome was the incidence of one or more medication therapy discontinuities. Outcome occurrence was assessed for the hospitalised and non-hospitalised group on the index date. For each patient, 6 control time points (6, 12 and 18 months prior and after the index date) were also defined. Drug use at each of these times was estimated on the basis of the theoretical duration of the prescriptions that had been dispensed by a community pharmacy before the specified date. The theoretical duration of use of each dispensed drug was estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs that had a theoretical end date beyond the index date or beyond 1 of the 6 control time points were considered as in use on these dates. Only drugs intended for systemic use were taken into account. Discontinuity was defined as no follow-up dispensing occurred within 4 months after the index date or after 1 of the 6 control moments. In the Netherlands drugs are usually prescribed for 30 days, although 90 days is

allowed, therefore a maximum follow-up period of 4 months seemed sufficient. Discontinuities in medication were classified into 4 mutually exclusive groups: (1) generic/brand substitution, (2) product substitution, (3) therapeutic switch and (4) stop (Appendix, p. **35**). Our classification implies that dispensing the same drug at a different daily dose, was not considered as a medication therapy discontinuity. Given the design of the study, new starts were not taken into consideration.

Data analysis

The number of patients with one or more medication therapy discontinuities was assessed on the index date and on the specified time points before and after the index date. The incidence rate of discontinuities was calculated for those patients using at least one drug on each of the different observation moments. To calculate the relative risk, the incidence of discontinuity in the hospitalised group of patients was compared with the incidence in the non-hospitalised group. To assess the effects of other factors associated with patient and hospitalisation characteristics, namely age, sex, duration of hospitalisation (1 day, 2-5 days, and > 5 days), admission type (emergency or planned admission), admission with a surgical indication or another indication and differences in health status as measured by the Chronic Disease Score (CDS), we performed a stratified and multivariate analysis for the medication used on the index date. The CDS is a measure of the chronic disease status among prescribed drug users and can be considered as an indicator of an individual's morbidity and overall health status. Exposure to various prescriptions drugs has shown to be a valid measure of certain chronic somatic diseases. (e.g., insulin as a proxy for diabetes mellitus). The score increases with the complexity of the drug regimen as well as the number and severity of 17 different chronic diseases.[16-18] All analyses were performed using SPSS 12.0 (SPSS, Chicago, IL).

Results

The study population comprised 10,000 patients admitted to the hospital and an equal number of matched non-hospitalised patients. Because of incomplete exposure history available in PHARMO RLS 1,319 patients were excluded, resulting in a final population of 8,681 patients. Table 1 provides the characteristics of the hospitalised patient group on the index date. Mean ± SD age was 52.6 year ± 21.8 years; 58.7% of the patients were female. The

patients in the hospitalised group were using more medications compared with the patients in the non-hospitalised group. The average number of drugs using at the index date was 3.0 versus 2.1. Likewise the CDS was higher in the hospitalised group than in the non-hospitalised group (e.g. CDS ≥ 4: 30.7% vs14.7% respectively). Hospital length of stay was divided into 3 categories: 1 day (4.8%), 2-5 days (50.4%) and >5 days (44.8%).

Figure 1 shows the incidence of the 4 different types of medication therapy discontinuities in the hospitalised and non-hospitalised group for each of the specified observation moments. At all time points, the incidence of a discontinuity was increased in the hospitalised group of patients compared with the non-hospitalised group.Except for the generic-brand substitution there was an elevation in the incidence of discontinuities in the hospitalised group on the index date. Of all hospitalised patients taking medication at the index date 63.1% had one or more medication therapy discontinuities at the index date compared with 33.5% of the non-hospitalised group taking medication at the index date. [RR 1.82 (95%CI 1.71-1.94)] (Table 2). In the hospitalised group of patients, the most frequent discontinuity at the index date was a stop (55.2%), followed by product substitution (7.9%), therapeutic switch (6.9%) and generic/brand substitution (4.7%). A relative risk was calculated for each of these specified discontinuities. The highest relative risk was found for a therapeutic switch [RR 5.34 (95%CI 3.93-7.26)], although this type of discontinuity occurred least frequently. There was no increased relative risk at the index date for generic/brand name substitution [RR 0.87 (95%CI 0.72-1.06)].

Table 1. Characteristics of the hospitalised patient group (n=8,681)

Characteristic		n	%
Sex	male	3,588	41.3
	female	5,093	58.7
Age (years at the index date)	65 years	5,557	64.0
	65-79 years	2,333	26.9
	≥ 80 years	791	9.1
Duration of hospitalisation	1 day	417	4.8
	2-5 days	4,374	50.4
	> 5 days	3,890	44.8
Admission type	emergency	3,966	45.7
	planned	4,715	54.3
Admission for surgery	yes	4,360	50.2
	no	4,321	49.8

Table 3 shows the association between hospitalisation and any medication therapy discontinuity at the index date, stratified by patient and characteristics of hospital stay. The relative risk increased with age and duration of hospitalisation and was slightly higher for men than for women. Patients admitted through the emergency department and those admitted for indications other than surgery were more vulnerable to discontinuity of pre-hospitalisation prescribed drugs.

Table 2. Incidence and relative risk (95% CI) of medication therapy discontinuities on the index date

	Hospitalised (n=8,681)	Non-hospitalised (n=8,681)	Crude R.R (95%CI)	Adjusted R.R. (95%CI)
Using no medication	3,416 (39.4%)	4,534 (52.2%)		
Using any medication	5,265 (60,6%)	4,147 (47.8%)		
Average # of drugs using at the index date	3.0	2.1		
Generic/brand substitution	245 (4.7%)	179 (4.3%)	1.08 (0.89-1.31)	0.87 (0.72-1.06)
Product substitution	418 (7.9%)	116 (2.8%)	2.84 (2.31-3.49)	2.32 (1.88-2.86)
Therapeutic switch	361 (6.9%)	47 (1.1%)	6.05 (4.46-8.20)	5.34 (3.93-7.26)
Stop	2,904 (55.2%)	1,133 (27.3%)	2.02 (1.89-2.16)	1.98 (1.85-2.13)

Discussion

The main finding of this study is that hospital admission was associated with an increased risk of medication therapy discontinuities, especially stops. Discontinuities are often based on rational decisions in order to optimize the patient's clinical condition. Given that hospitalisation often is the result of a worsening in the patient's condition, many discontinuities in medication therapy are intended. Of the 4 classifications of discontinuities used in this stydy, stops were observed most frequently. Intended reasons for stopping use of a drug can be because the prescribed drug was unnecessary, ineffective or contributing to toxicity or adverse reactions. In some cases, prescribed drugs may include those for witch clinical efficacy has not been proven or those that are not listed in the local formulary for reasons other than pharmacological issues.[19] Medication stops can also be intended when drugs are prescribed not for chronic use but rather for a limited time, as with antibiotics and analgesic

Table 3. Stratified analyses of any medication therapy discontinuity at the index date

	Hospitalised			Non-hospitalised			
	# of patients	# of patients with ≥ 1 discontinuation	Incidence (%)	# of patients	# of patients with ≥ 1 discontinuation	Incidence (%)	RR (95%CI)**
Overall	5265	3322	63.1	4147	1390	33.5	1.88 (1.77-2.00)
Sex							
Male	1994	1289	64.6	1349	438	32.5	1.99 (1.83-2.16)
Female	3271	2033	62.2	2798	952	34.0	1.83 (1.72-1.94)
Age							
< 65	2740	1639	59.4	2186	786	36.0	1.66 (1.56-1.77)
65-79	1222	789	64.6	949	280	29.5	2.19 (1.97-2.44)
≥ 80	1303	894	68.6	1012	324	32.0	2.14 (1.95-2.36)
CDS*							
0	1283	703	54.8	1531	528	34.5	1.59 (1.46-1.73)
1-3	1526	896	58.7	1462	478	32.7	1.80 (1.65-1.96)
≥ 4	2457	1723	70.1	1154	384	33.3	2.11 (1.93-2.30)
Duration of hospitalisation							
Non hospitalisation				4147	1390	33.5	Reference
1 day	235	146	62.1				1.85 (1.66-2.07)
2-5 days	2347	1287	54.8				1.64 (1.55-1.73)
> 5 days	2683	1889	70.4				2.10 (2.00-2.21)
Admission type							
Non hospitalisation				4147	1390	33.5	Reference
Emergency	2422	1737	71.7				2.14 (2.04-2.25)
Planned	2843	1585	55.7				1.66 (1.58-1.76)
Surgery							
Non hospitalisation				4147	1390	33.5	Reference
Yes	2389	1335	55.9				1.67 (1.58-1.76)
No	2876	1987	69.1				2.06 (1.96-2.17)

* CDS = Chronic Disease Score

** RR = Relative Risk

medications. However, this intended discontinuity will likely occur in the same frequency in the hospitalised as well as in the non-hospitalised group

of patients. Unintended reasons for stopping drug use often result from miscommunication about a patient's therapy at the time of hospital admission. Relatively, hospitalisation was most frequently associated with therapeutic switches. This finding may imply that during hospitalisation important reasons occur for switching one drug to another drug within the same therapeutic class. This could be the result of therapeutic considerations or due to hospital drug formularies conversions. Changing drug regimen during hospital stay to comply with institutional formulary requirements may contribute to patient confusion and miscommunication with other health care providers. While patients are on a certain drug regimen upon admission to a hospital, they may be discharged on another. According to Beers *et al*, situations in witch drugs are stopped and replaced with similar medications can also indicate that hospital physicians believe that better alternatives are available.[20] In the event that several suppliers of the same drug are available, the rate of switching between available drugs would be an additional factor for discontinuity.

There was no association between hospitalisation and a switch between a generic and brand name drugs. Generic-brand name substitution will not always be classified as a discontinuity. Nevertheless these substitutions can be considered as a determinant for medication errors given the confusion that these changes can cause to the patient. Hospital drug formularies are often different from community drug formularies within a certain region. These formularies differ not only with respect to the choice of the active substances but also with respect to the choice of type of brand for the same active substance. Generally speaking, in the Netherlands original brands are more frequently used inside the hospital because of the price discounts on these products and because of the availability of a larger spectre of product forms. In the community setting, generic prescribing and dispensing are encouraged by government policy.[21] Once the patient is discharged the community pharmacy may replace, if available, the brand drug used in the hospital with a generic drug that was used before admission. This finding is in accordance with a previous study by our group, where we found a 20% generic substitution of the last clinical medication upon hospital discharge.[22] Several studies conclude, that discontinuation of drug use at hospitalisation is seen frequently.[1,23,24] Despite the different settings, these studies also found a 50-60% discontinuity of drug use at hospital discharge. Admissions for surgical indications have a lower relative risk for discontinuities than for non surgical admissions. In general internal medicine

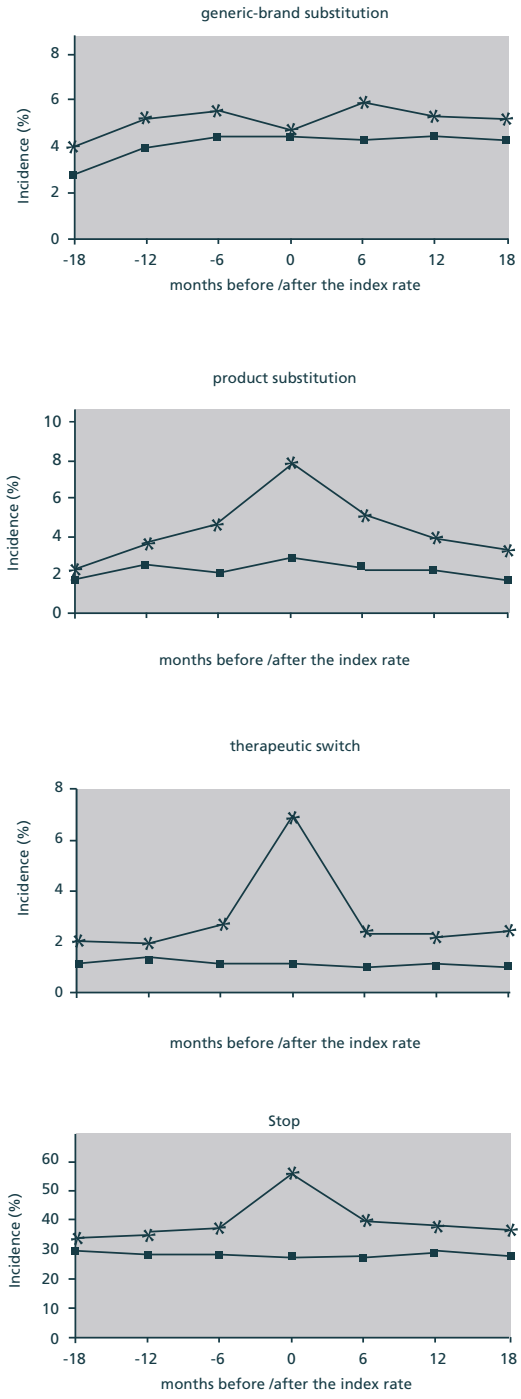


Figure 1. Incidence of medication therapy discontinuities at the different observation moments

(-X- = hospitalised patients; -■- = nonhospitalised patients)

patients are prescribed more drugs than patients with a surgical indication and more intended medication changes are to be expected. Also emergency admissions are more vulnerable for discontinuities than planned admissions. We need to consider the potential limitations of this study. Non-hospitalised patients were sampled from a group of subjects who were dispensed drugs during the study period. It is likely that this control group is in general less sick than the group of hospitalised patients, which can be explained by the difference in the number of drugs used by the two groups. As no diagnoses regarding the hospital stay were available, we were not able to detect drug induced hospitalisations. These admissions often requires therapeutic interventions with intended discontinuities in drug use. Special attention has to be given to unintended medication discontinuities. In general the clinical and therapeutic monitoring of patients after discharge significantly declines.[25] In view of the increasing trend for earlier discharges, the need to ensure continuity of care (seamless care) is likely to have significant impact on quality health outcomes. Therefore, patients should not be discharged until the details of the medication changes and arrangements for follow up have been communicated to other healthcare providers, who are responsible for the patients ongoing care.[26] Medication reconciliation at 'interfaces of care' can be an effective and efficient method for identifying medication discontinuities and preventing inappropriate changes in medication use.[27-30]

Conclusions

This is the first longitudinal study in a large group of patients over a period of 36 months to document the association between hospitalisation and medication therapy used in the community setting. We found a strong association between hospitalisation and medication therapy discontinuities, especially stops. Hospital safety programs should focus attention on medication therapy discontinuities at times of transition to ensure continuity of pharmaceutical care. Medication reconciliation should be done at every transition of care in order to avoid medication errors.

References

1. Grimmsmann T, Schwabe U, Himmel W. The influence of hospitalisation on drug prescription in primary care – a large-scale follow-up study. Eur J Clin Pharmacol 2007;63:783-90
2. Smith JD, Coleman EA, Min S-J. A new tool for identifying discrepancies in postacute medications for community dwelling older adults. The American Journal of Geriatric Pharmacotherapy 2004;2:141-7
3. The ASHP Continuity of care task force. Continuity of care in medication management: review of issues and considerations for pharmacy. Am J Health-Syst Pharm 2005;62:1714-20
4. 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;173:510-5
5. Tisnado DM, Adams JL, Liu H *et al*. What is the concordance between the medical record and patient self-report as data sources for ambulatory care. Med Care 2006;44:132-40
6. Cornish PL, Knowles SR, Marchesano R *et al*. Unintended medication discrepancies at the time of hospital admission. Arch Intern Med 2005;165:424-9
7. Himmel W, Lönker B, Kochen MM. Non-formulary drug requests at an academic hospital in Germany-the role of general practitioners long-term medication. Eur J Clin Pharmacol 1998;54:41-6
8. Himmel W, Tabache M, Kochen MM. What happens to long-term medication when general practice patients are referred to hospital. Eur J Clin Pharmacol 1996;50:253-7
9. Van Hessen PAW, Petri H, Urquhart J. Do prescribed drugs always follow the patient to hospital. Pharm Weekbl [Sci] 1990;12:66-70
10. Coleman EEA, Smith JD, Raha D, Min S-J. Post hospital medication discrepancies, prevalence and contributing factors. Arch Intern Med 2005;165:1842-7
11. Van der Linden CMJ, Kerskes MCH, Bijl AMH, Maas HAAM, Egberts ACG, Jansen PAF. Represcription after adverse drug reaction in the elderly: a descriptive study. Arch Intern Med 2006;166:1666-7
12. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med 2003;138:161-7
13. Boockvar K, Fishman E, Kyriacou CK, Monias A, Gavi S, Cortes T. Adverse events due to discontinuation in drug use and dose changes in patients transferred between acute and long-term care facilities. Arch Intern Med 2004;164:545-50

14. Omori DM, Potyk RP, Kroenke K. The adverse effects of hospitalisation on drug regimes. Arch Intern Med 1991;151:1562-4
15. Herings RMC, Bakker A, Stricker BHC, Nap G. Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. J Epidemiol Community Health 1992;46:136-40
16. Korff M von, Wegner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992;45:197-203
17. Clark DO, Von Korff M, Saunders K, Baluch WM, Simon GE. A chronic disease score with empirically derived weights. Med Care 1995;33:783-95
18. Johnson RE, Hornbrook MC, Nichols GS. Replicating the chronic disease score from automated pharmacy data. J Clin Epidemiol 1994;47:1191-9
19. Bradley CP. Factors which influence the decision whether or not to prescribe: the dilemma facing general practitioners. Br J Gen Pract 1992;42:454-8
20. Beers MH, Dang J, Hasegawa J, Tamai IY. Influence of hospitalisation on drug therapy in the elderly. J Am Geriatr Soc 1989;37:679-83
21. Fijn R, Brouwers JRBJ, Knaap RJ, De Jong-Van Den Berg LTW. Drug and therapeutics committees in Dutch hospitals: a nation-wide survey of structure, activities and drug selection procedures. Br J Clin Pharmacol 1999;48(2):239-46
22. Stuffken R, Egberts ACG. Discontinuities in drug use upon hospital discharge. Pharmacy World & Science 2004;26:268-70
23. Kripalani S, Jackson AT, Schnipper JL, Coleman EA. Promoting effective transitions of care at hospital discharge: a review of key issues for hospitalists. J Hosp Med 2007;2:314-23
24. Moore C, Wisnivesky J, Williams S, McGinn T. Medical errors related to discontinuity of care from an inpatient to an outpatient setting. J Gen Intern Med 2003;18:646-51
25. Egger SS, Drewe J, Schlienger R G. Potential drug-drug interactions in themedication of medical patients at hospital discharge. Eur J Clin Pharmacol2003;58:773-8
26. Australian Pharmaceutical Advisory Council. National guidelines to achieve the continuum of quality use of medicines between hospital and community Canberra, Australia: Commonwealth Department of Health and Family Services, 1998
27. Vira T, Colqujoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. Qual Saf Health Care 2006;15:122-6
28. Pronovost P, Weast B, Schwarz M *et al.* Medication reconciliation: a practical tool to reduce the risk of medication errors. J. Critical Care 2003; 18:201-5

29. Rodehaver C, Fearing D. Medication reconciliation in acute care: ensuring an accurate drug regimen on admission and discharge. Jt Comm J Qual Patient Saf 2005; 31:406-13
30. Nickerson A, MacKinnon NJ, Roberts N, Saulnier L. Drug therapy problems, inconsistencies and omissions identified during a medication reconciliation and seamless care services. Healthcare Quart 2005;8:65-72

Appendix: Classification of types of discontinuities

Classification	Definition
Generic - brand substitution	change to another product containing the same active substance with the same strength and the same dosage form e.g. atenolol 50mg tablet (generic product) instead of Tenormin® 50mg tablet (brand) or Renitec® 10mg tablet (brand) instead of enalapril 10 mg tablet.
Product substitution	change to a drug containing the same active substance but a different strength and/or dosage form e.g. enalapril 10mg tablets instead of enalapril 20mg tablet or metoprolol 50mg plain tablet instead of metoprolol slow release tablet (Selokeen ZOC®)
Therapeutic switch	change to another substance within the same therapeutic group; the first 4 characters of the ATC classification are the same, e.g. amitriptyline (N06AA09) instead of citalopram (N06AB04) or fluoxetine (N06AB03) instead of citalopram
Stop	no continuation after the index date of the use of an individual drug and not one of the other discontinuations

Chapter 2.2

DISCONTINUITIES IN DRUG USE UPON HOSPITAL DISCHARGE

Rutger Stuffken
Toine C.G. Egberts

PharmWorld Sci 2004;26(5):268-70

Abstract

Objective

To investigate the nature and frequency of changes in drug treatment upon discharge from hospital.

Method

All drugs of discharged patients, dispensed by an outpatient pharmacy were compared with the latest clinical medication and discontinuities were classified.

Results

Of all prescriptions, dispensed by the outpatient pharmacy, 40% had some discontinuity; most frequent were product substitution (27%) and new prescriptions, starting at the moment of discharge (11%).

Conclusion

There is a gap in the conformity between drugs used in the hospital and the drugs dispensed by the outpatient pharmacy at the moment of discharge.

Introduction

Medical errors are a major cause of harm to patients.[1] Medication errors and adverse drug reactions have recently received a lot of attention in the professional and lay press. [2,3] Many of these drug-related problems seem to be systematic in origin and preventable. A transition between different echelons in health care (*e.g.* from hospital to home care) may be a risk factor in such problems, especially if changes in prescribed drug regimen occur during such transitions.[4] Continuity of care (seamless care) is the desired end-product of the hospital discharge process and is essential to the optimisation of drug-related outcomes. Inconsistencies can result in patient confusion and the supply of misinformation to the community. Interventions that improve continuity of care between hospital pharmacies and community pharmacies have been associated with improved clinical outcomes and avoidance of drug related problems.[5]

Previously published research has demonstrated that drug use several weeks after discharge often deviates from the drug treatment at the moment of discharge.[6,7] Drug-drug interactions with combinations that potentially may result in major clinical consequences at discharge are frequently the result of changes of the prescription medication during hospitalisation.[8] Little research, however, has been conducted on the conformity of drug use in the hospital and the drugs delivered at the moment of discharge.

Hospital drug formularies are often different from community drug formularies within a certain region. These formularies differ not only with respect to the choice of the active substances but also with respect to the choice of type of brand for the same active substance. Generally speaking, in the Netherlands original brands are more frequently used inside the hospital because of the price discounts on these products and because of the availability of a larger spectrum of product forms, whereas outside the hospital, generic prescribing and dispensing is encouraged by government policy. Such discrepancies in drug policy between the hospital and the outpatient setting may contribute to discontinuities in the patient's drug use.

The aim of the present study was to investigate the nature and frequency of discontinuities in drug treatment in a cohort of patients discharged from the hospital and characteristics associated with it.

Method

Setting

This was a study conducted in the Hilversum Hospital, a 489-bed general hospital. The Hilversum Hospital has two pharmacies; a hospital pharmacy and an outpatient one. The hospital pharmacy delivers the medicines only for hospitalised patients, whereas the outpatient pharmacy is comparable with a community pharmacy.

All patients discharged from the hospital have the opportunity to choose to receive their prescribed drugs from the outpatient pharmacy located inside the hospital or from a community pharmacy.

Study design

Included were all patients discharged from the hospital during the month of May 2001 and who presented one or more prescriptions from the medical specialist in the hospital's outpatient pharmacy. Excluded from the study were patients who had been in the hospital for one day only.

All drugs dispensed by the outpatient pharmacy were compared with the patient's latest clinical medication to establish discontinuities in prescribing. Discontinuities were classified either as therapeutic switch, product substitution or start of a new drug (Table 1).

Table 1. Classification of discontinuities

Classification	Definition
Therapeutic switch	Another therapeutic substance in the same group; the first 4 characters of the ATC classification are the same, e.g. amitriptyline in stead of citalopram or fluoxetine in stead of citalopram
Product substitution	Same active substance e.g. atenolol in stead of Tenormin®, and same active substance but different in strength or formulation e.g. ciprofloxacine 250 mg tablets in stead of 500 mg tablets.
New drug	The first prescription of the drug is upon discharge from the hospital

All medicines were classified into therapeutic groups using the Anatomical Therapeutic Chemical Classification system (ATC) of the WHO Collaborating Centre for Drug Statistics.
In addition, all discharge medicines dispensed by the outpatient pharmacy were classified as prescriptions in conformity with the hospital drug formulary (HDF). Non-adherence to the drug formulary could exist on two levels: the active substance was in the HDF but in the form of a different product, or the active substance was not in the HDF at all. The HDF used in the Hilversum Hospital, can be regarded as 'restrictive', meaning that non-formulary prescriptions are not honoured in principle.[9]

Data-analysis

Data were compiled from each patient's pharmaceutical record as well as the record from the hospital pharmacy and the record from the outpatient pharmacy. These data were entered in a Microsoft Access database and statistically analysed with SPSS for Windows version 9.0 (SPSS, Inc., Chicago, Illinois).

Result

During the study period (May 2001) 954 patients were discharged from the hospital, of whome 227 (24%) received their drugs from the outpatient pharmacy and thereby constituted the study population. Mean age was 61 year (range 1 month - 95 year); 50.7% were female. The total number of prescriptions dispensed was 684; the average number for each discharged patient was 3 prescriptions (range 1 – 13).
The vast majority of prescriptions originated for patients discharged from internal medicine (27.5%), cardiology (16.7%), pulmonology (14.5%) and orthopaedics (9.9%).
The medication dispensed at discharge was in conformity with the latest clinical medication in 412 of the 684 prescriptions (60.2%), i.e. no discontinuity (Table 2). The most frequently observed discontinuity was product substitution (27%; n=185), of which 137 (74.1%) prescriptions concerned generic substitution (e.g. from a brand name drug to a generic drug). A few products were responsible for the majority of the generic substitutions. The most frequently observed substitutions were Sintrom mitis® to acenocoumarolum and Ascal® to carbasalatum-calcium. Of the drugs, 77 (11.3%) drugs concerned a new prescription, i.e. starting with discharge from the hospital.

Overall, 66.2% of the drugs dispensed by the outpatient pharmacy were conform with the HDF; 5.7% concerned an active substance not listed in the HDF, 28.1% concerned a different product for an active substance listed in the HDF. The dispensing of active substances not listed in the HDF was more frequently observed in newly started prescriptions (10.4%) than in patients with another discontinuity (4.1%) (p=0.047; chi-square).

Table 2. Frequency and classification of prescriptions (n=684)

Classification of discontinuity	Number (%)
No discontinuity	412 (60.2)
Therapeutic switch	10 (1.5)
Product substitution	185 (27.0)
New drugs	77 (11.3)

Discussion

Hospital discharge may be associated with relevant changes in patient care. Our study showed that at at the moment of discharge a substantial number of discontinuities in drug use occur in comparison with drug use during hospitalisation. Most discontinuities seem minor changes from a treatment point of view. There seems to be no link between local outpatient prescribing or delivering policy and hospital drug formulary and government policy with respect to reimbursement between the inpatient and outpatient setting. Recently, much attention has been given to drug-related problems and it has been suggested that suboptimal communication between different health care providers may be a contributing factor. In the Netherlands it is government policy to encourage the dispensing of generic products. Pharmacists are permitted to dispense the often cheaper generic product, even if the physician prescribes a brand name. Inside the hospital, brand name products are more frequently used than generic products. Drug companies sell their drugs to the hospitals at discount prices to ensure the drug will be placed in the Hospital Drug Formulary. The impact of hospital prescribing on prescribing in general practice is substantial and has been documented.[10] In contrast with dispensing patterns in the hospital, our outpatient

pharmacy mostly dispenses a generic drug, when available. In this study, upon discharge from hospital we found a 20.0% generic substitution of the last clinical medication, half of which is due to two drugs. Although the brand-name product and a generic product contain the same active substance, they may appear completely different to the patient, which, without adequate information, can lead to sub-optimal use by the patient. As result of this study and anticipating the development of a regional drug formulary, in the Hilversum Hospital, we replaced some brand name drugs by generic drugs. The amount of reimbursement for drugs in the Netherlands is fixed by the government. There is the strange phenomenon that one dosage form of a drug can be excluded from full reimbursement, while another dosage form is not excluded. This will be the main reason for changing the dosage form when the outpatient pharmacy does the dispensing. This way the patient gets the drug free of charge, but in the transition between hospital and home care this change may be a risk factor for errors.

Early study showed that in the Hilversum Hospital the Hospital Drug Formulary is largely followed in the outpatient clinic.[11] In this study we found, that 19 of 20 prescriptions are in accordance with the hospital drug formulary with respect to the active substance.

Our results are not necessarily representative of the overall Dutch situation. The small scale of this study, involving only the prescription pattern of the physicians of one hospital and the dispensing pattern in one outpatient pharmacy, limits the generalizability of the results. However, recent study conducted in Germany showed similar results.[12] Nevertheless, the present results demonstrate the importance of closer communication between all health care professionals to ensure the continuity of treatment.

Conclusions

In conclusion, our study highlights the changes in treatment that can occur at discharge from the hospital into the community.
Preventing medication errors is a major topic; the key issue is to have the right information about actual drug use at the moment of admission or discharge from the hospital. There is therefore a strong need to get the availability of one

electronic medical file of each patient, including relevant information with respect to drug use.

Nevertheless, the adequate information, the development of a regional drug formulary has to be stimulated, so that there is not only conformity on the level of the active substance, but also on the level of the dispensed brand name or generic name drugs.

References

1. Kohn LT, Corrigan JM, Donaldson MS, To err is human: Building a safer health system. Committee on Quality of Health Care in America, Institute of Medicine, National Academy Press Washington; 2000
2. Van den Bemt PMLA, Egberts ACG, De Jong-Van den Berg LTW, Brouwers JRBJ. Drug related problems in hospitalised patients. Drug Safety 2000; 22: 321-3
3. Fijn R, Van den Bemt PMLA, Chow M, De Blaey CJ, De Jong-Van den Berg LTW, Brouwers JRBJ. Hospital prescribing errors: epidemiological assessment of predictors. Br J Clin Pharmacol 2002; 53: 326-31
4. Forster AJ, Murff HJ, Peterson JF *et al*. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med 2003; 138: 161-7
5. Cameron B. The impact of pharmacy discharge planning on continuity of care. Can J Hosp Pharm 1994; 47(3): 101-9
6. Cochrane RA, Mandal AR, Ledger-Scott M, Walker R. Changes in drug treatment after discharge from hospital in geriatric patients. BMJ 1992; 305: 694-6
7. Himmel W, Tabache M, Kochen MM. What happens to long-term medication when general practice patients are referred to hospital? Eur J Clin Pharmacol 1996; 50: 253-7
8. Egger SS, Drewe J, Schlienger RG. Potential drug-drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol 2003; 58: 773-8
9. Fijn R, Lenderink AW, Egberts ACG, Brouwers JRBJ, De Jong-Van den Berg LTW. Assessment of indicators for hospital drug formulary non-adherence. Eur J Clin Pharmacol 2001;57: 677-84
10. Bijl D, Van Sonderen E, Haaijer-Ruskamp FM. Prescription changes and drug costs at the interface between primary and specialist care. Eur J Clin Pharmacol 1998 ; 54: 333-6
11. Stuffken R, Egberts ACG, van Schaik BAM. Insight in specialistic prescription writing. Registration of outpatient medication and discharge medication. Pharm Weekbl 2001;136(11):390-4
12. Taxis K, Schneeweiss S. Frequency and predictors of drug therapy interruptions after hospital discharge under physician drug budgets in Germany. Int J Clin Pharmacol Therap 2003; 41: 77-82

Chapter 2.3

THE ASSOCIATION BETWEEN HOSPITALISATION AND DISCONTINUITY OF PSYCHOTROPIC DRUG USE

Rutger Stuffken
Patrick C. Souverein
Toine C.G. Egberts
Eibert R. Heerdink

Abstract

Background

Hospitalisation is an event that has been shown to increase patients' risk of discontinuity of pharmacotherapy. In particular medication unrelated to the reason for hospital admission may be at risk of discontinuity. This hypothesis is tested by analyzing changes in psychotropic drug treatment in patients hospitalised for a non-psychiatric reason.

Methods

The subjects were patients who were admitted to hospital for a non-psychiatric disorder and who were using psychotropic drugs (antipsychotics, antidepressants or benzodiazepines). For each hospitalised patient, one non-hospitalised patient was sampled. The outcome was measured as the incidence of one or more medication discontinuities of psychotropic drugs at hospitalisation (index date) and 6 control moments. 3 mutually exclusive types of discontinuities were defined: stop, substitution and therapeutic switch.

Results

Of 444 hospitalised patients on a psychotropic drug regimen at the index date, 140 (31.5%) had a medication discontinuity in their use of psychotropic drugs, compared to 49 (16.2%) discontinuities in the 303 non-hospitalised patients (adjusted RR 1.92; 95% CI 1.39 – 2.66). The predominant discontinuity was stop (27.5% in hospitalised vs 11.2% in the non-hospitalised patients). The highest risk estimate for any discontinuity was seen in antipsychotics (adjusted RR 6.28; 95% CI 2.28 - 17.7).

Conclusion

Patients admitted to hospital for a non-psychiatric disease while using psychotropic medication are at increased risk for discontinuity of the psychotropic medication. Stopping medication especially of antipsychotics was seen most often.

Introduction

Discontinuities in medication therapy often occur when patients transition from one healthcare setting to another.[1-4] Our group has previously described an association between hospital admissions and the risk of discontinuities in medication used in the community setting. [5] Up to 63% of all hospitalised patients discontinued one or more medications that were used before hospitalisation. Most frequently seen discontinuity at hospitalisation was stopping of medication (55%). Treatment during admission to the hospital includes the evaluation of present drug regimens, so some of the discontinuities of medication were presumably intended and explicable. However, a significant number of changes occurred in medication unrelated to the reason for hospital admission and are therefore likely to be unintended.[6] A potential consequence of such changes is that unintended discontinuities in drug therapy may worsen clinical outcomes.

Over the last decennia there has been a general trend towards increased use of psychotropic drugs, and therefore increasing numbers of patients admitted to hospitals will be using psychotropic medication. In general, when a patient is admitted to hospital for a non-psychiatric disease, there will be no therapeutic reason for the physician to change or discontinue psychotropic drug therapy, except when a patient is admitted for reasons arising from side effects of psychotropic drug use. Continuous use of psychotropic drugs at therapeutic doses is an important goal for the treatment of psychiatric disorders, and discontinuities in these medications is considered a negative outcome that can worsen the psychiatric outcome.[7] Lack of knowledge about these specific drugs or lack of information about the reasons for prescribing them can be a cause of intentional or unintentional discontinuity. To the best of our knowledge, no study has been carried out to evaluate the discontinuities of drug use unrelated to the reason for hospitalisation. This study aims to investigate this issue and directly test the hypothesis that the use of psychotropic medication unrelated to the reason for hospital admission is at increased risk for discontinuation.

Methods

Setting

This study was performed using data collected during regular patient care processes as available from the PHARMO Record Linkage System (RLS; www.pharmo.nl). The PHARMO RLS includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all two

million community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 to the present.[8] Briefly, the computerized drug dispensing histories contain information concerning the drug dispensed, date of dispensation, physician, amount dispensed, and prescribed dosage regimen. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system. Patient information includes sex and date of birth. Each patient is registered with an anonymous and unique patient identification code that allows for the observation of a patient's drug therapy over time. The hospital discharge records include detailed information concerning the primary and secondary discharge diagnoses according to the International Classification of Diseases, 9th edition (ICD) [http://icd9cm.chrisendres.com/], as well as diagnostic, surgical, and treatment procedures. The type and frequency of consultation with medical specialists, and the dates of hospital admission and discharge were also included. The database does not provide information concerning the indication for use of the medicines or the complete registration of non-prescription products, as individuals may also purchase these drugs from non-pharmacy outlets.

Study population

A retrospective follow-up study was conducted. Initially, 10,000 patients who had been hospitalised between July 1, 1998 and June 30, 2000 were randomly selected from the PHARMO RLS. The date of admission was termed the index date. For each hospitalised patient, one non-hospitalised patient of the same age, sex and geographic area was sampled and assigned the same index date as that of the corresponding hospitalised patient. Only patients for whom medication data were available for 24 months before and after the index date were eligible. Patients who were admitted for mental disorders (ICD-9-CM code 290-319) were excluded. To analyze changes in psychotropic drug use those patients using a psychotropic drug on at least one of the observation time points were selected.

Table 1. Classification of types of discontinuities

Classification	Definition
stop	no continuation after the index date or 1 of the 6 control time points.
product substitution	change to a drug containing the same active substance but strength or dosage form are different. (e.g. paroxetine 20-mg tablets instead of paroxetine 30-mg tablet or amitriptyline plain tablet instead of amitriptyline slow release tablet) or generic-brand substitution.
therapeutic switch	change to a drug containing another active substance within the same therapeutic group; the first 4 characters of the ATC classification are the same. (e.g. amitriptyline (N06AA09) instead of citalopram (N06AB04) or fluoxetine (N06AB03) instead of citalopram

ATC = Anatomical Therapeutic Chemical

Outcome

The primary outcome of this study was the incidence of one or more medication therapy discontinuities of psychotropic drugs. Psychotropic drugs were defined as drugs of the ATC group N05A (antipsychotics) and N06A (antidepressants). Outcome occurrence was assessed for the hospitalised and the non-hospitalised group on the index date as well as on 6 control time points (6, 12, and 18 months prior to and after the index date). Psychotropic drug use at each of these time points was estimated on the basis of the theoretical duration of the prescriptions that had been dispensed by a community pharmacy before the specified date. The theoretical duration of use of each dispensed drug was estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs that had a theoretical end date beyond the investigated time points were considered as in use on those dates. Discontinuation was defined as no follow-up dispensing of the same prescribed drug occurring within 4 months after the index date or after one of the 6 control time points (*Figure 1*). In the Netherlands, drugs are usually prescribed for 30 days, although 90 days is allowed; therefore, a maximum follow-up period

of 4 months was deemed sufficient for this study. Discontinuities in the use of medication were classified into 3 mutually exclusive groups: stop (1), product substitution (2) or therapeutic switch (Table 1). According to our classification scheme, dispensing the same drug with the same strength at a different daily dose was not considered a discontinuity. Given the design of the study, initiation of new therapy was not taken into consideration. A secondary outcome of this study was the incidence of represcription in the subgroup of patients in whom psychotropic use was stopped on the index date. A represcription was defined as a prescription of a drug of the same Anatomical Therapeutic Group (ATC 5) and was recorded when a drug was stopped during hospitalisation and represcribed in the time window of 4-12 months after the index date.

Data analysis

The number of patients with one or more discontinuities of psychotropic drugs use was assessed on the index date and on the specified time points before and after the index date. The incidence rate of discontinuities was calculated for patients using a psychotropic drug on at least one of the different observation moments. To calculate the relative risk, the incidence of discontinuity in the hospitalised group of patients was compared to the incidence in the non-hospitalised group. To assess the effects of other factors a stratified analysis according to age, sex, duration of hospitalisation (1, 2-5, > 5 days), admission type (emergency or planned and surgical or a non-surgical indication) was performed. Furthermore, the psychotropic drugs were stratified into antipsychotics and antidepressants and a stratified and multivariate analysis on the index date was conducted. The rate of represcription of psychotropic medication was calculated as the incidence of restart for the hospitalised group of patients. All analyses were performed using SPSS 16.0 (SPSS, Chicago, IL).

Results

The study population comprised 10,000 patients admitted to the hospital and an equal number of matched non-hospitalised patients. Because of incomplete exposure history available in PHARMO RLS, 1,319 patients were excluded from the initial study population. Exclusion of patients who were admitted for mental disorders resulted in a final population of 8,555 hospitalised patients and an equal number of controls. At each of the seven time points a different

number of patients were using one or more psychotropic drugs. In the hospitalised group of patients psychotropic medication was prescribed more frequently (Figure 2). Figure 2 also shows the incidence of the 3 different types of medication therapy discontinuities in the hospitalised and non-hospitalised group for each of the specified observation time points. Stopping medication at the index date was the only discontinuity that was significantly higher in the hospitalised patients compared to the controls. Of all the hospitalised patients with psychotropic drug therapy on the index date (n = 444) 140 (31.5%) had a medication discontinuation of psychotropic drugs, compared with (n=303) 49 (16.2%) of the non-hospitalised patient group (adjusted RR 1.92; 95% CI 1.39- 2.66) (Table 2). A relative risk was calculated for each of the specified discontinuities on the index date. There was no significant difference for product substitution (adjusted RR 0.68; 95% CI 0.27-1.73) and therapeutic switch (adjusted RR 0.99; 95% CI 0.35-2.79), while medication stop was significantly increased (adjusted RR 2.42; 95% CI 1,65-3.54) (Table 2). Table 2 shows the outcome occurrence according to the stratification by patient, hospitalisation and medication characteristics. The highest risk estimate was found for antipsychotics (adjusted RR 6.28; 95% CI 2.28 – 17.7), followed by antidepressants (adjusted RR 1.47; 95% CI 1.03 – 2.10). Subgroup analyses on the index date revealed that female patients, elderly patients, patients admitted for an emergency admission, and non surgical patients had an increased risk for discontinuities in the use of psychotropic drugs.

Of all psychotropic prescriptions on the index date (n= 497), 132 prescriptions were stopped. The represcription rate of these withdrawn medication in the time window of 4-12 months after hospitalisation was 23.5% for drugs of the same therapeutic class.

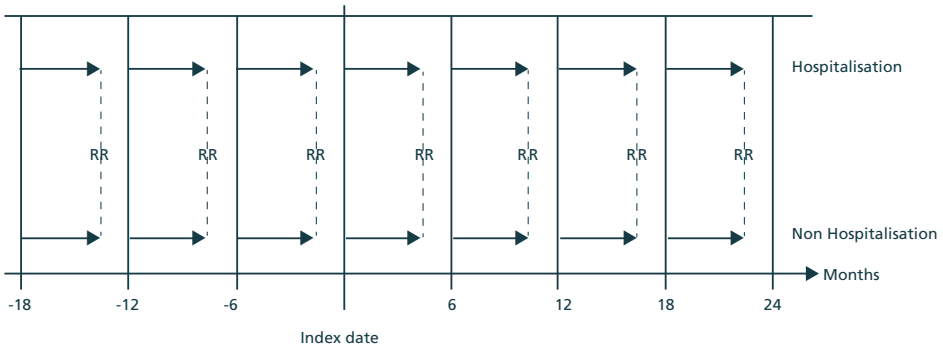
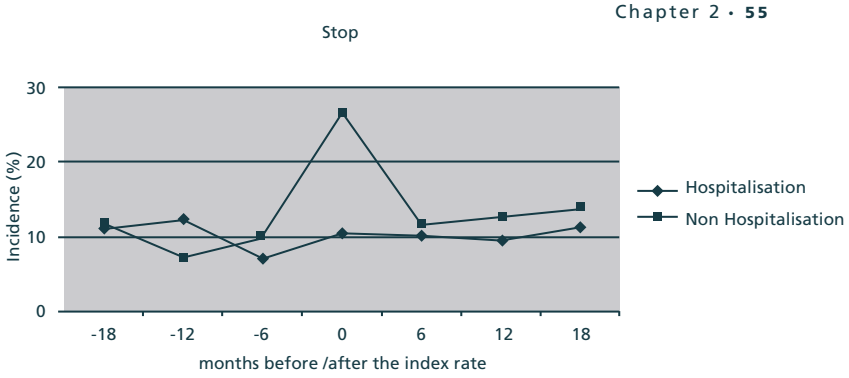


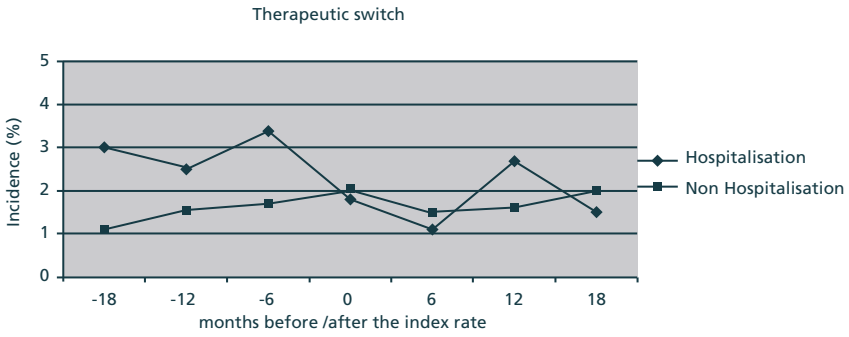
Figure 1. Discontinuities in drugs used on the index date as well as 6,12 and 18 months before and after the index date

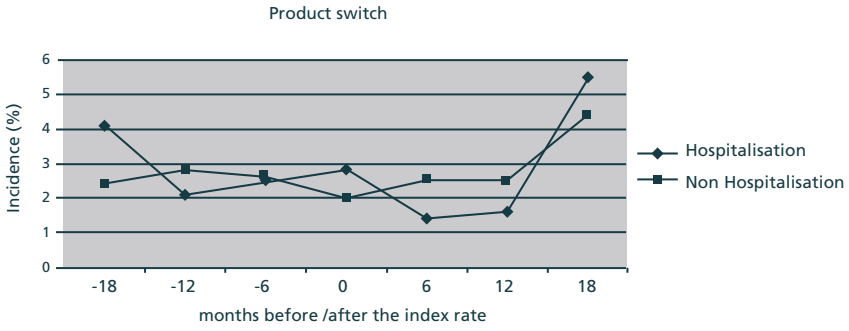
Discussion

The main finding of this study was that hospital admission for a non-psychiatric disease is associated with an increased risk of discontinuity in psychotropic medication. Of all the classifications of discontinuities described in this study, stops were predominantly observed. Within this discontinuity the subgroup of antipsychotics had the highest risk of discontinuity and was significantly higher than the subgroup of antidepressants.

Changes to drug regimens are often made during hospitalisation.[9,10] Intentional reasons for stopping drug use can be because the prescribed agent was unnecessary, ineffective, contributing to toxicity or adverse drug reactions or the prescribed drug was not listed in the local hospital formulary. [11] Medication stops can also be intended when drugs are prescribed for a limited time rather than for chronic use as with antibiotics and analgesics. Unintended reasons for stopping drug use often result from miscommunication about a patient's drug therapy. [12,13] Unintentional discontinuity of drug use can also be the result of lack of accurate knowledge about specific drugs or lack of information about the reasons for prescribing them. In this study we analyzed the discontinuity of a specific group of drugs namely psychotropic drugs. These drugs are regularly prescribed for continuous use. In daily practice, admission of a patient to the hospital for reasons that are unrelated to the conditions for which these medication are prescribed should not result in changes to the patient's established psychotropic drug regimens. However, we found a 6-fold increase in incidence of the stop-discontinuity for antipsychotics in this group







months before/ after the index date	-18	-12	-6	0	6	12	18
#psychotropic prescription (hospitalised)	380	399	459	497	475	486	497
# psychotropic prescription (non-hospitalised)	268	285	325	325	363	367	398

Figure 2. **Incidence of medication therapy discontinuities at the different observation moments**

Table 2. Incidence and Relative Risk (95% CI) of medication therapy discontinuities at the Index Date (t=0)

	Hospitalised patients using psychotropic drugs (n=444, incidence %)	Non-hospitalised patients using psychotropic drugs (n=303, incidence %)	Crude R.R. (95%CI)	Adjusted RR (95% CI) Adjusted for age and sex
No discontinuity	304 (68.5%)	254 (83.8%)	reference	reference
Any discontinuity	140 (31.5%)	49 (16.2%)	1.95 (1.41-2.70)	1.92 (1.39-2.66)
Stop	122 (27.5%)	34 (11.2%)	2.45 (1.67-3.58)	2.42 (1.65-3.54)
Therapeutic switch	9 (2.0%)	6 (2.0%)	1.02 (0.36-2.88)	0.99 (0.35-2.79)
Product substitution	9 (2.0%)	9 (3.0%)	0.68 (0.27-1.71)	0.68 (0.27-1.73)
Stratified analysis (any change/total %)				
Female	55/143 (38.5%)	10/80 (12.5%)	3.08 (1.57-6.04)	3.06 (1.56-6.01)
Male	85/301 (28.2%)	39/223 (17.5%)	1.61 (1.11-2.36)	1.61 (1.10-2.35)
<65 years	69/248 (27.8%)	34/174 (19.5%)	1.42 (0.94-2.15)	1.42 (0.94-2.14)
65-80 years	26/92 (28.3%)	7/53 (13.2%)	2.14 (0.93-4.93)	2.09 (0.91-4.81)
≥80 years	45/104 (43.3%)	8/76 (10.5%)	4.11 (1.94-8.72)	4.16 (1.96-8.84)
1 drug used	114/398 (28.6%)	44/282 (15.6%)	1.83 (1.30-2.60)	1.81 (1.28-2.56)
>1 drug used	26/46 (56.5%)	5/21 (23.8%)	2.37 (0.91-6.18)	2.39 (0.91-6.27)
Use of antipsychotics*	35/94 (37.2%)	4/71 (5.6%)	6.61 (2.35-18.60)	6.28 (2.28-17.7)
Use of antidepressants*	100/360 (27.8%)	44/235 (18.7%)	1.48 (1.04-2.11)	1.47 (1.03-2.10)
Use of other psychotropics*	11/18 (61.1%)	1 /10 (10.0%)	6.11 (0.79-47.3)	5.92 (0.74-47.4)
1 day hospitalisation**	7/25 (28.0%)	49/303 (16.2%)	1.73 (0.78-3.82)	1.72 (0.77-3.80)
1-5 days hospitalisation**	49/191 (25.7%)	49/303 (16.2%)	1.59 (1.07-2.36)	1.57 (1.05-2.34)
>5 days hospitalisation**	84/228 (36.8%)	49/303 (16.2%)	2.28 (1.60-3.24)	2.28 (1.60-3.26)
Emergency admission**	79/200 (39.5%)	49/303 (16.2%)	2.44 (1.71-3.49)	2.41 (1.68-3.45)
Planned admission**	61/244 (25.0%)	49/303 (16.2%)	1.55 (1.06-2.25)	1.53 (1.05-2.23)
Surgery**	45/192 (23.4%)	49/303 (16.2%)	1.44 (0.97-2.17)	1.44 (0.96-2.16)
No surgery**	95/252 (37.7%)	49/303 (16.2%)	2.33 (1.65-3.29)	2.30 (1.62-3.25)

* totals add to more than 100% due to multiple drug use

** compared to the total control group

of patients. In conclusion, patients using antipsychotic medication who are admitted to the hospital for a non-psychiatric disease are at high risk for discontinuity of these drugs.

Discharge requires adequate transfer of information about medication prescribed at discharge and information about reasons for the discontinuation of drug therapy. The loss of information due to poor communication between hospitals and primary care physicians can result in represcription of medications that has been stopped intentionally during hospital admission. [14,15] Within the same therapeutic class, 23.5% of the psychotropic drug treatments that were stopped during hospitalisation were represcribed within a time window of 4-12 months after hospitalisation. These findings confirm the results of the study of Van der Linden et al. who found a rate of represcription of withdrawn medication of 27% during the first 6 months after discharge. The scope and limitations of this study need to be considered when discussing the present results. First, the database does not provide information concerning the indication of use. Another limitation of the present study is that physicians may fail to write a prescription for each change in drug use. The only data available for identifying prescription changes were the dispensing data from the community pharmacies. Therefore, the association between hospitalisation and discontinuity of psychotropic drug use could have been underestimated. Furthermore, the data set used in this study covered a time period between July 1998 and June 2000. Although unlikely, it is possible that during the past ten years, the prescribing behaviour of physicians could have been influenced by medication reconciliation programs.[16,17] Hospital admission rates could have decreased in the last ten years as well, due to cuts, medical innovations, and stricter indications for admissions. Subsequently, this could lead to an overestimation of the results. No data were available concerning the socio-economic status of the patients in the study and issues related to compliance with therapy could not be taken into account. In summary, hospitalisation for a non-psychiatric disease has a significant impact on the continuity of psychotropic medication, especially antipsychotics. Hospital safety programs should focus attention on medication discontinuities at times of transition to ensure continuity of care with respect to drug therapy. Physicians should be aware of the reasons of prescribing psychotropic medication. Reasons of intended changes in medication unrelated to the reason of hospital admission should be described in a discharge summary.

References

1. Climente-Marti M, Garcia-Mañón EG, Artero-Mora A, Jiménez-Torres NV. Potential risk of medication discrepancies and reconciliation errors at admission and discharge from an inpatient medical service. Ann Pharmacother 2010;44:1747-1754
2. Coleman EA, Berenson RA. Lost in transition: Challenges and opportunities for improving the quality of transitional care. Ann Intern Med 2004;140:533-6
3. Coleman EA, Smith JD, Raha D, Min S-J. Posthospital Medication Discrepancies, Prevalence and Contributing Factors. Arch Intern Med. 2005;165:1842-7
4. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchels EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ. 2005;173:510-5
5. Stuffken R, Heerdink ER, de Koning FHP, Souverein PC, Egberts ACG. Association between hospitalisation and discontinuity of medication therapy used in the community setting in the Netherlands. An Pharmacother 2008;42:933-9
6. Unroe KT, Pfeiffenberger T, Riegelhaupt S, Jastrzembski J, Lokhnygina T, Colón-Emeric C. 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;8:115-126
7. Huyse FJ, Touw DJ, Strack van Schijndel R, de Lange JJ, Slaets JPJ. Psychotropic drugs and perioperative period: a proposal for a guideline in elective surgery. Psychosomatics 2006;47:8-22
8. Herings RMC, Bakker A, Stricker BHC, Nap G. Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. J Epidemiol Community Health 1992;46:136-140
9. Grimes TC, Duggan CA, Delaney TP, Graham IM, Conlon KC, Deasy E, Jago-Byrne MC, O'Brien P. Medication details documented on hospital discharge: cross-sectional observational study of factors associated with medication non-reconciliation. Br J Cl Pharmacol 2011;71:3:449-457
10. Himmel W, Kochen MM, Sarns U, Hummers-Pradler E. Drug changes at the interface between primary and secondary care. Int J Cl Pharmacol Ther 2004;42:103-9
11. Himmel W, Tabache M, Kochen MM. What happens to long-term medication when general practice patients are referred to hospital. Eur J Clin Pharmacol 1996;50:253-7

12. Glintborg B, Andersen SE, Dalhoff K, Insufficient communication about medication use at the interface between hospital and primary care. Qual Saf Health Care 2007;16:34-9
13. Kripalani S, LeFevre F, Philips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians. JAMA 2007;297:831-841
14. Van der Linden CMJ, Jansen PAF, Van Geerenstein EV, van Marum RJ, Grouls RJE, Egberts ACG, Korsten EHM. Reasons for discontinuation during hospitalisation and documentation thereof: a descriptive study of 400 geriatric and internal medicine patients. Arch Intern Med 2010; 170:1085-7
15. Van der Linden CMJ, Kerskes MCH, Bijl AMH, Maas HAAM, Egberts ACG, Jansen PAF. Represcription after adverse drug reaction in the elderly: a descriptive study. Arch Intern Med. 2006;166:1666-7
16. Vira T, Colqujoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. Qual Saf Health Care 2006;15: 122-6
17. Karapinar-Carkit F, Borgsteede SD, Zoer J, Smit HJ, Egberts ACG, van den Bemt PMLA. Effect of medication reconciliation with and without patient counseling on the number of pharmaceutical interventions among patients discharged from the hospital. Ann Pharmacother 2009;43:1001-10

THE IMPACT OF HOSPITALISATION ON THE INITIATION AND LONG-TERM USE OF BENZODIAZEPINES

Rutger Stuffken
Rolf P. van Hulten
Eibert R. Heerdink
Kris L.L. Movig
Toine C.G. Egberts

Eur J Clin Pharmacol 2005; 61(4):291-5

Abstract

Background

Inappropriate (long-term) use of benzodiazepines (BZDs) is a reason for concern. Several studies have suggested that hospitalisation may be a determinant for initiation of BZD use as well as for long-term use. However, the available evidence is conflicting.

Objective

To determine whether hospitalisation induces initiation of benzodiazepine use and subsequent long-term use.

Methods

A retrospective follow-up study was conducted. Randomly, 10,000 patients, who had been hospitalised were selected (index date). Non-hospitalised patients, matched on age and sex, were sampled from the same living region and assigned the same index date as the corresponding hospitalised patient. Patients were included if adequate medication data were available from 18 months before until 18 months after the index date. Initiation of benzodiazepine use was defined as a prescription for a benzodiazepine or benzodiazepine-related hypnotic without a prescription for any of these drugs during the prior 6 months. Long-term use was defined as a period of consecutive use for at least 6 months following initiation.

Results

In this study 8,681 hospitalised patients and an equal number of non-hospitalised patients were finally included. Overall, the relative risk for initiation of benzodiazepine use was almost twice as high (IDR 1.97 [95%CI 1.84-2.10]) among hospitalised patients as in non-hospitalised patients. This relative risk was most clearly elevated during the time window from 3 months before to 3 months after hospitalisation (IDR 4.81 [95%CI 4.08-5.67]). The relative risk for long-term use during the entire 36 months observation period was not higher (IDR 1.04 [95%CI 0.95-1.13]) among hospitalised patients than among non-hospitalised patients. Within the time window of 3 months before and after hospitalisation, the relative risk for long-term use was significant lower for the hospitalised group (RR 0.82 [CI 0.69-0.98]).

Conclusion

Our results confirm that hospitalisation is associated with an increased risk for initiation of benzodiazepine use; the risk is highest in the 3 months just before and after hospitalisation. However, hospitalisation appeared not to be a determinant for long-term use of benzodiazepines.

Introduction

Benzodiazepines are widely prescribed drugs for the treatment of several psychiatric disorders. Insomnia and anxiety are generally accepted indications for these agents. However, considerable controversy surrounds the use of benzodiazepines. These drugs are frequently used over longer periods of time, and this has been addressed in several studies.[1,2] Long-term use has been associated with increased risk of dependence and withdrawal symptoms upon discontinuation.[3,4] In the elderly the use of benzodiazepines has been associated with an increased morbidity risk.[5] Short-term use is associated with an increased risk of injury-related mortality. [6,7] It has been accepted that enduring benzodiazepine use is inappropriate for the treatment of anxiety states or insomnia.[8]

Hospitalisation is often a major life-changing event that may provoke anxiety and insomnia; hospitalisation itself can be a reason for initiation benzodiazepine use. It has been suggested that benzodiazepine use started during hospital stay is an important factor for community use of these drugs. Howes *et al.* found that of all hospital admissions and not previously taken benzodiazepines resulted in 23.6% in a prescription for a benzodiazepine for the first time in the hospital and, in 5.3% of these patients, this resulted in a benzodiazepine prescription at discharge.[9] First prescriptions do lead to more benzodiazepine prescriptions within a limited amount of time.[10] Although the impact of hospitalisation with regard to the initiation of benzodiazepine prescriptions has been well documented, data about the relationship between hospitalisation and benzodiazepine use remain conflicting and have not always addressed potential biases arising from possibly important confounders such as health status.[11,12,13,14,15]

The objective of our study was to evaluate the possible association between hospitalisation and the initiation of benzodiazepine use in ambulatory care in the pre-and post hospitalisation periods. Because hospitalisation may also lead to unnecessary long term continuation of benzodiazepine use, we calculated the period of consecutive use of benzodiazepine use after the initial prescription and thereby also evaluated the possible association between hospitalisation and long-term use.

Methods

Setting

The setting of the study was the PHARMO record linkage system. PHARMO includes pharmacy dispensing records from community pharmacies linked to hospital discharge diagnoses of all 950,000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 onwards. This database has been described in full elsewhere.[16]

In brief, the computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system for benzodiazepines (N05BA and N05CD) and benzodiazepine-related hypnotics and sedatives i.e. zolpidem and zopiclone (N05CF).

Patient information per prescribed medicine includes sex and date of birth. Each registered person is identified with an anonymous unique identification code that allows for the observation of patient medication use in time. The database does not provide information concerning the indication for use of the medicines nor the complete registration of non-prescription medicines as patients may also purchase these drugs from non-pharmacy outlets.

The hospital discharge records are obtained from PRISMANT, previously known as the Dutch Center for Healthcare Information (LMR Database), an institute that collates nationwide all hospital discharge records in the Netherlands since the 1960s into a standardised format. Relevant hospital data include the primary and secondary discharge diagnoses and data of hospital admission and discharge.

Study population

A retrospective follow-up study has been conducted. In this study initially 10,000 patients who had been hospitalised (index date) between July 1st 1998 and June 30th 2000 were randomly selected from the PHARMO database. For each hospitalised patient we sampled from the same living region a patient matched on age and sex, who had not been hospitalised during the same period. Patients were only included in this study if medication data for the time window of 18 months before and 18 months after the index date were available.

Because of the lack of these medication data over the whole study period, some patients had to be excluded. The final study population consisted therefore of 8,681 patients and an equal number of matched non-hospitalised patients.

Outcome

Primary outcome was the initiation of benzodiazepine use which was determined within a time window of 18 months before and 18 months after the index date and was defined as a prescription for a benzodiazepine (ATC N05BA and N05CD) or benzodiazepine-related hypnotic or sedative (ATC N05CF) in this time window and not having had a prescription for any of these drugs in a time period of 6 months before that date. Secondary outcome was long-term use of benzodiazepines following the initial prescription. Long-term use was defined as a period of consecutive use of these drugs of more than 180 days as determined from the date of the initial prescription.[17] Patients were followed up until the estimated duration of use for the last benzodiazepine prescription for each individual patient with a maximum of 6 months.

Data analysis

The data were analysed in two ways; first incidence density rates and ratios of initiation of benzodiazepine use were calculated in the total study population as well as for the time window of 3 months before and after hospitalisation. We determined the number of first benzodiazepine prescriptions and calculated the incidence rate of first benzodiazepine prescriptions per 100 patient-years. The incidence rate of the hospitalised group of patients was compared to the incidence of the non-hospitalised group. The relative risk was expressed as the incidence density ratio (IDR), in which the non-hospitalised group was taken as a baseline risk. In order to assess the effects of other factors associated with patient and hospitalisation characteristics, namely age, sex, duration of hospitalisation, admission type, admission for surgery and differences in health status, we performed a stratified analysis in the time window of 6 months. The health status was measured with the Chronic Disease Score (CDS). This is a measure of the chronic disease status among prescribed drug users and can be considered as an indicator of an individual's morbidity and overall health status. Valid measures of chronic disease status can be obtained from patients' medical records, but abstracting medical records is costly and difficult. The use of automated out-patient pharmacy databases appears to offer an increasingly available and low-cost approach to developing a measure of CDS. Exposure

to various prescriptions drugs has shown to be a valid measure of certain chronic somatic diseases. (e.g., insulin as a proxy for diabetes mellitus). The score ranges increases with the complexity of drug regimen as well as the number and severity of 17 different chronic diseases.[18-20] Benzodiazepines and other psychotropic drugs are not included in the CDS.

Results

The study population consisted of 8,681 hospitalised patients and an equal number of non-hospitalised patients. Table 1 provides the characteristics of the hospitalised patient group on the index date. Mean age was 52.6 year (S.D. 21.8) and 58.7% of the patients were female. The patients in the hospitalised group were using more medications than the patients in the non-hospitalised group (CDS = 0, [42.2% versus 60.0%] and CDS ≥ 4, [30.7% versus. 14.7%]. During the entire study period, the incidence density (ID) of initial benzodiazepine prescription in the hospitalised group was 11.8 per 100 patient years (2,436/20,613 pyrs) and in the non-hospitalised group 6.0 per 100 patient years (1,396/23,249 pyrs). Initiation of benzodiazepine use was therefore twice (IDR 1.97 [95%CI 1.84-2.10]) as high in the hospitalised group compared to the non-hospitalised group.

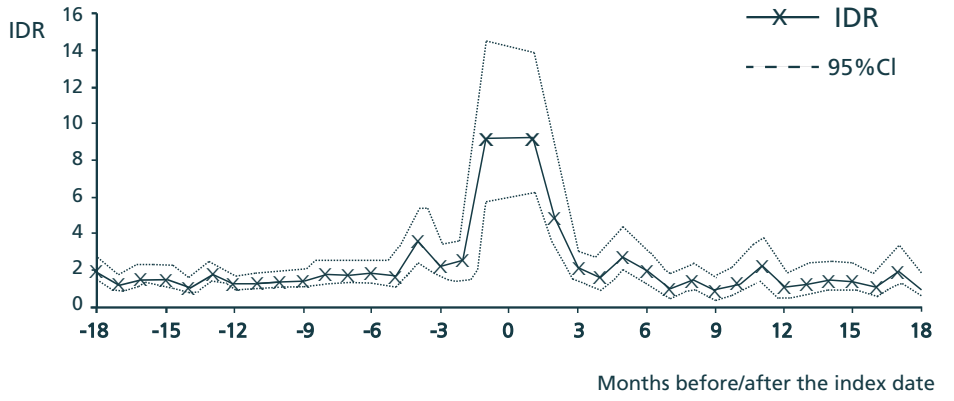


Figure 1. Incidence density ratio (IDR) of initiation benzodiazepine use 18 months before and after hospitalisation compared with that in non-hospitalised patients

Table 1. Characteristics of the hospitalised patient group (n=8681) on the index date

Characteristic		n	(%)
Sex	male	3,588	41.3
	female	5,093	58.7
Age (years on index date)	<65 years	5,557	64.0
	≥ 65 years	3,124	36.0
Duration of hospitalisation	1 day	417	4.8
	2-5 days	4,374	50.4
	> 5 days	3,890	44.8
Admission type	emergency	3,966	45.7
	planned	4,715	54.3
Admission for surgery	yes	4,360	50.2
	no	4,321	49.8

Table 2. Benzodiazepines and benzodiazepine related hypnotics as initial prescription

	Number of starts (%)	
	Hospitalised	**Not hospitalised**
	(n=8681)	**(n=8681)**
Any	2,436 (28.1%)	1,396 (16.1%)
Anxiolytics (N05BA)		
Diazepam	579 (6.7%)	303 (3.5%)
Oxazepam	701 (8.1%)	519 (6.0%)
Other	181 (2.1%)	109 (1.3%)
Total	**1,461 (16.8%)**	**931 (10.8%)**
Hypnotics (N05CD and N05CF)		
Nitrazepam	71 (0.8%)	53 (0.6%)
Temazepam	684 (7.9%)	287 (3.3%)
Other	220 (2.5%)	125 (1.4%)
Total	**975 (11.2%)**	**465 (5.3%)**

In the hospitalised group 16.8% of the total study group initially used anxiolytics and 11.2% hypnotics (table 2); in the non-hospitalised group these percentages were 10.7% and 5.4% respectively. For both types of benzodiazepines we therefore observed a similar increased risk of initiation of these drugs in the hospitalised group compared with to the non-hospitalised group.

Figure 1 shows the monthly IDR for starting a benzodiazepine prescription during the study period of 36 months. The IDR was most clearly elevated during the time window of 3 months before and after hospitalisation (IDR 4.81 [95%CI 4.08-5.67]). Table 3 presents in that time window of 6 months the association of hospitalisation and initiation of benzodiazepine use stratified by patient and hospitalisation characteristics. Incidence rates increased with age and duration of hospitalisation and were higher for men than for women. Patients with more medication (i.e. CDS ≥ 4) are more likely to receive a first benzodiazepine prescription. The relative risk for long-term use (more than 180 days) in the entire 36 month period was slightly, non significantly higher (RR 1.04 [95%CI 0.95-1.13]) among hospitalised patients than among non-hospitalised patients (58.5% of all initial benzodiazepine prescriptions in hospitalised patients group were categorized as long-term medication vs. 56.2% in the non-hospitalised group). Within the time window of 3 months before and after hospitalisation the relative risk for long-term use was significantly lower for the hospitalised patient group (RR 0.82 [95%CI 0.69-0.98]).

Table 3. **Results of starting benzodiazepine use during the time window of 3 months before and after hospitalisation compared with those in non-hospitalised patients**

	Hospitalised			Non-hospitalised			
	# of starts	Follow-up (pyrs)	Incidence (per 100 pyrs)	# of starts	Follow-up (pyrs)	Incidence (per 100 pyrs)	IDR (95%CI)
Overall	728	3198	22.8	174	3676	4.7	4.81 (4.08-5.67)
Sex							
Female	410	1859	22.1	119	2110	5.6	3.91 (3.19-4.80)
Male	318	1340	23.7	55	1566	3.5	6.76 (5.08-9.00)
Age							
<65	433	2103	20.6	119	2347	5.1	4.06 (3.32-4.97)
>=65	295	1095	26.9	55	1329	4.1	6.51 (4.88-8.68)
CDS							
0	257	1447	17.8	89	2257	3.9	4.50 (3.54-5.73)
1-3	227	851	26.7	62	896	6.9	3.86 (2.91-5.11)
>=4	244	900	27.1	23	524	4.4	6.18 (4.03-9.47)
Duration of hospitalisation							
				174	3676	4.7	Reference
1 day	25	158	15.8				3.34 (2.20-5.08)
2-5 days	271	1663	16.3				3.44 (2.85-4.16)
> 5 days	432	1377	31.4				6.63 (5.59-7.90)
Admission type							
				174	3676	4.7	Reference
Emergency	357	1453	24.6				5.19 (4.33-6.22)
Planned	371	1745	21.3				4.49 (3.75-5.38)
Surgery							
				174	3676	4.7	Reference
Yes	303	1664	18.2				3.85 (3.19-4.64)
No	425	1534	27.7				5.85 (4.91-6.98)

Discussion

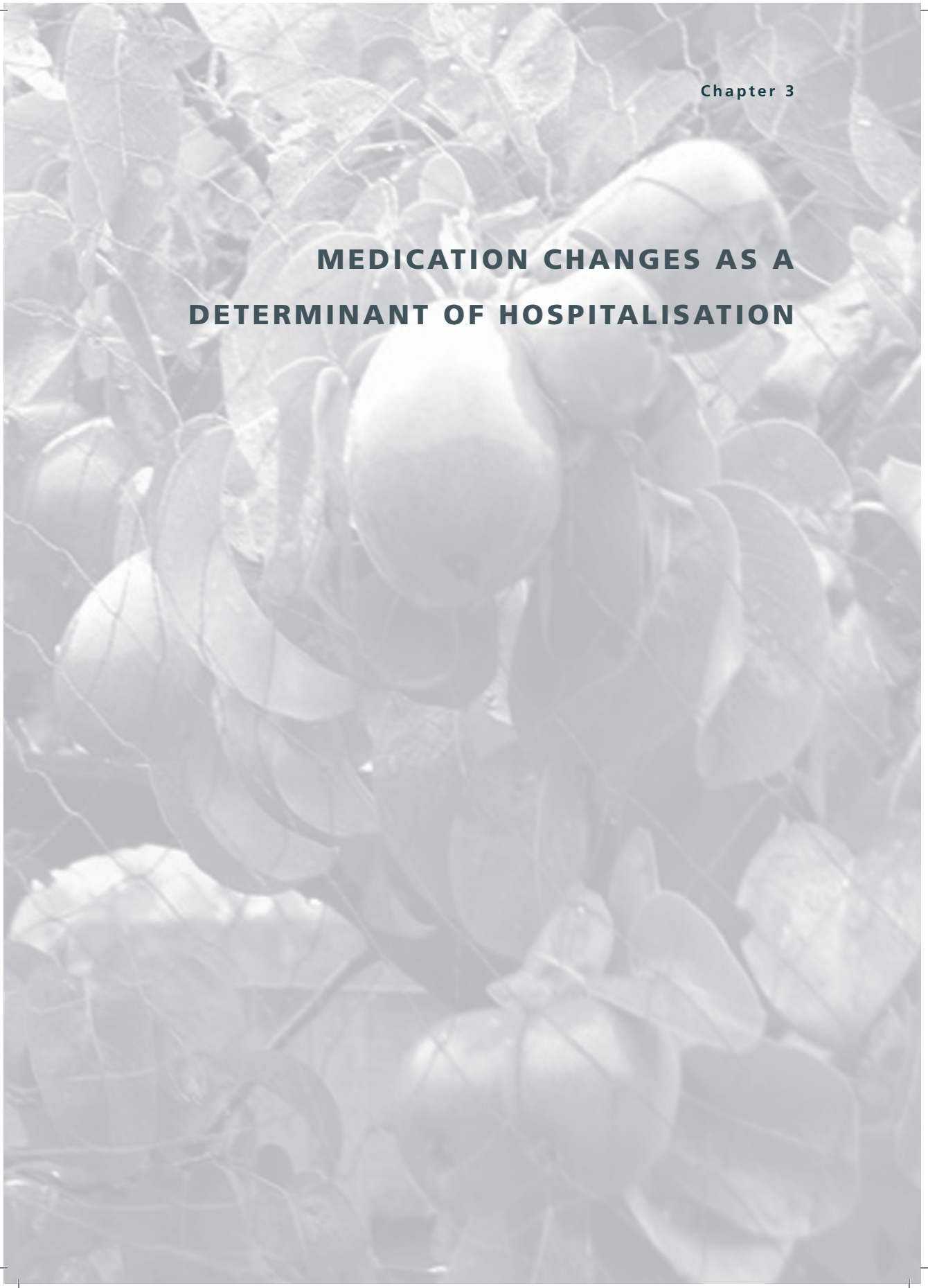
In this study we examined first benzodiazepine prescriptions not only after discharge from the hospital, but also during a pre-hospitalisation period. We calculated the monthly IDR for starting a benzodiazepine prescription over the whole study period of 36 months. One of the most interesting findings of this study is the strong association between hospitalisation and initial prescriptions of benzodiazepines in the time window of 3 months before and after admission with an IDR of 4.81. Our findings agree with several other studies, which have reported an association between hospitalisation and hospital initiated and newly ambulatory prescribed benzodiazepines.[9,11-14] In contrast to these studies, we were also able to asses the relationship between hospitalisation and newly prescribed benzodiazepines before hospitalisation. Problems with physical health can have an impact on mental health.[21] Accordingly, mental manifestations linked to an underlying physical disease may manifest first. Van Hulten *et al.* found that benzodiazepines are a predictor for the onset of chronic disease.[22] Probably deterioration of the health status, leading to later hospitalisation was the reason for starting benzodiazepines. We can therefore not conclude that hospitalisation causes (unnecessary) benzodiazepine initiation as has been suggested by others.[14], but that the time period around a hospitalisation is associated with new benzodiazepine use. Further research is necessary to elucidate the underlying reasons for this fascinating pattern. Stratified analyses during the 3 month period before and after hospitalisation demonstrates, that the risk of an initial benzodiazepine prescription was modified by patient and hospitalisation characteristics. Patients who use more medication (i.e. patients with a CDS ≥ 4) are more likely to receive a first benzodiazepine prescription. These findings agree with other studies, which have reported that benzodiazepine use is more common among subjects with poor health status.[23] Sex has been found to be a significant factor in predicting benzodiazepine use in many studies and is more prevalent among female.[24,25] We observed the same pattern in the non-hospitalised group. However, we found in the period of 3 months before and after hospitalisation that the relative risk for benzodiazepine initiation was higher for men than for women. We analysed the cumulative exposure months after the initial prescription. There was a significant lower risk for long-term use of a benzodiazepine in the time window of 3 months before and after the hospitalisation date, compared with the whole study period. We could therefore not confirm findings of others that hospitalisation is also associated with (unnecessary) longterm use of

benzodiazepines We need to consider the potential limitations of this study, when interpreting the present results. In this study, non-hospitalised patients were sampled from a group of subjects who were dispensed any drug in the study period. It is likely that this control group is in general less sick than the group of hospitalised patients, which could at least partly explain the increased use of benzodiazepines by this group. Therefore we measured in both groups the chronic disease score and stratified on this (Table 3). This might, however, not have eliminated all differences in health status. Our definition of the initial prescription of a benzodiazepine (no prescription without a previous 6 months of use) might imply that several initial users could have been previous user in earlier months before our time window. That possibility might result in some misclassification and thereby slightly overestimation of our results. In conclusion, previous studies have raised much concern about hospitalisation-related initiation of benzodiazepine use and about long term use of these drugs. The present study reveals that hospitalisation contributes to a clearly increased risk for initiation a benzodiazepine prescription. The risk is highest in the 3 months just before and after hospitalisation. Sex, age, chronic disease score and duration of hospitalisation are factors influencing the probability of starting with a benzodiazepine related to hospitalisation. We could not show an association between hospitalisation and the risk for long-term use.

References

1. Salinsky JV, Doré CJ, Characteristics of long term benzodiazepine users in general practice. J Royal Coll Gen Pract (1987)37:202-4
2. Isacson D, Long-term benzodiazepine use: factors of importance and the development of individual use patterns over time; a 13-year follow-up in a Swedish community. Soc Sci Med (1997) 44:1871-80
3. Marriott S, Tyrer P, Benzodiazepine dependence: avoidance and withdrawal. Drug Safety (1993) 9(2):93-103
4. Tyrer P, Murphy S, The place of benzodiazepines in psychiatric practice. Br Psychiatry (1987) 151:719-723
5. Vinkers DJ, Gussekloo J, van der Mast RC, Zitman FG, Westendorp RGJ, Benzodiazepine use and risk of mortality in individuals aged 85 years or older. (2003) JAMA 290:2942-3
6. Neutel CI, Hirdes JP, Maxwell CJ, Patten SB, New evidence on benzodiazepine use and falls: The time factor. Age Ageing (1996) 25:273-8
7. Wagner AK, Fang Zhang F, Soumerai SB, Walker AM Gurwitz JH, Glynn RJ *et al*, Benzodiazepine use an Hip Fractures in the Elderly. Arch Intern Med (2004) 164: 1567-1572
8. Committee on the Review of Medicines Systematic review of the benzodiazepines. BMJ (1980) 280:910-2
9. Howes JB, Ryan J, Fairbrother G, O'Neill K, Howes LG, Benzodiazepine prescribing in a Sydney teaching hospital. MJA (1996) 165:305-8
10. Neutel CI, Maxwell CJ, The benzodiazepine treadmill. Does one prescription lead to more. Pharmacoepidemiology and drug safety (1996) 5:39-42
11. Grad R, Tamblyn R, Holbrook AM, Hurley J, Feightner J, Gayton D, Risk of a new benzodiazepine prescription in relation to recent hospitalisation. J Am Geriatr Soc (1999) 47:184-8
12. Millar HL, Clunie FS, Mc Gilchrist MM, Mc Mahon AD MacDonald T, The impact on community benzodiazepine prescribing of hospitalisation. J Psychosom Res (1997) 42:61-9
13. Shan K, Nolan JA, Turner P, Jackson SHD, Prescription of benzodiazepines in a London teaching Hospital. J of the Royal Society of Medicine (1990) 83:306-7
14. Surendrakumar D, Dunn M, Roberts CJC, Hospital admission and start of benzodiazepine use BMJ (1992) 304: 881

15. Wagner AK, Soumerai SB, Zhang F, Mah C, Simoni-Wastila L, Cosler L, *et al*, Effects of state surveillance on new post-hospitalisation benzodiazepine use. Int J for Quality in Health Care (2003) 15:423-431
16. Herings RMC, Bakker A, Stricker BHC, Nap G, Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. J Epidemiol Community Health (1992) 46:136-140
17. Rolf van Hulten, Hubert G Leufkens, Albert Bakker, Usage pattern of benzodiazepines in a dutch community: A Ten-Year Follow-Up. Pharmacy World & Science (1998) 20:78-82
18. Korff M von, Wegner EH, Saunders K A, chronic disease score from automated pharmacy data. J Clin Epidemiol (1992) 45:197-203
19. Clark DO, Von Korff M, Saunders K Baluch WM, Simon GE, A chronic disease score with empirically empirically derived weights. Med Care (1995) 33:783-795
20. Johnson RE, Hornbrook MC Nichols GS, Replicating the chronic disease score from automated pharmacy data. J Clin Epidemiol (1994) 47:1191-9
21. Editorial, Can treating depression improve disease outcomes. Annals of Internal Medicine (2004) 140: 1054-6
22. Rolf van Hulten, Eibert R. Heerdink, Albert Bakker, Hubert G. Leufkens, Benzodiazepines pathways in the chronically ill. Pharmacoepidemiology and Drug Safety (1999) 8: 325-330
23. Laurier C, Dumas J, Gregoire J-P, Factors related to benzodioazepine use in Quebec A secondary analysis of survey data. J Pharmacoepidemiol (1992) 4:73-86
24. Van der Waals FW, Mohrs J, Foets M, Sex differences among recipients of benzodiazepines in Dutch general practice. BMJ (1993) 307: 363-6
25. Morabia A, Fabre J, Dunand J-P, The influence of patient and physician sex on prescription of psychotropic drugs. J Clin Epidemiol (1992) 45: 111-6



Chapter 3

MEDICATION CHANGES AS A DETERMINANT OF HOSPITALISATION

Chapter 3.1

PRESCRIPTION CHANGE INTENSITY AND HOSPITALISATION

Carolien G.M. Sino
Rutger Stuffken
Eibert R. Heerdink
Marieke J. Schuurmans
Patrick C. Souverein
Toine C.G.Egberts

Abstract

Objective

Several risk factors for hospital admission have been established. Knowledge of risk factors may help to avoid potential preventable drug-related complications like hospital admissions. To assess the association between the intensity of prescription changes (PCI) and hospital admissions and to compare the PCI to the Chronic Disease Score (CDS).

Method

We recruited randomly 10.000 patients from the PHARMO database, who had been hospitalised (index date) between July 1, 1998 and June 30, 2000. For each hospitalised patient, one nonhospitalised patient was matched for age, sex, and geographic area, and was assigned the same index date as the corresponding hospitalised patient. The primary study outcome was the number of prescription changes during several 3-month time periods starting 18, 12, 9, 6, and 3 months before the index date. Odds ratios between hospitalised and non-hospitalised patients were calculated for each PCI category and compared to CDS score categories. We classified 4 mutually exclusive types of prescription changes: change in dosage, switch, stop and start.

Results

The study population comprised 8,681 hospitalised patients and an equal number of matched nonhospitalised patients. The odds ratio of hospital admission increased with an increase in Prescription Change Intensity (PCI) category. At 3 months before the index date from PCI =1 OR 1.4 [95%CI 1.3-1.5] to PCI= 2-3 OR 2.2 [95%CI 1.9-2.4] and to PCI ≥ 4 OR 4.1 [95%CI 3.1-5.1]. A higher CDS score was also associated with an increased risk of hospital admission.

Conclusions

The intensity of prescription changes (PCI) is associated with hospital admission. The PCI score could function as an independent warning signal for increased hospitalisation risk. Nurses and other healthcare workers should be alert when the intensity of prescription changes increases. Clinical rules could be helpful to make physicians and pharmacist aware of the risk of the number of prescription changes.

Introduction

Medication-related problems are responsible for 3-10% of acute hospital admissions, of which approximately half are potentially preventable. [1-11] Hospital admissions can lead to additional functional decline, unintentional harm and are expensive. Medication monitoring and medication management are both methods employed to avoid medication-related complications. Medication monitoring is part of a broader concept called medication management, which is basically a nursing intervention described by Bulecheck *et al.* [12] as follows: 'medication management is the promotion of a safe and effective use of prescribed and OTC medication, and a process of promoting and involving service users in treatment decisions, exchanging information and monitoring, evaluating and providing feedback about treatment'.

In 2008, the Dutch HARM study group established seven independent risk factors of medication-related hospital admissions: (1) impaired cognition, (2) 4 or more diseases in the patient's medical history, (3) dependent living situation, (4) impaired renal function before hospitalisation, (5) non-adherence to medication regimen, (6) the use of five or more medications at the time of admission (polypharmacy), and (7) age over 65 [11]. In the industrialised world, the proportion of the population that is 65 years of age or older is rapidly increasing. Elderly patients more frequently suffer from multi morbidities, use more medication and are treated by a larger number of health care professionals [13]. Drug consumption is 3 times higher among persons of 65 years or older, while people aged 75 years or older consume 4 times more. These drugs are mostly taken chronically (www.SFK.nl). Besides, due to longer life, increasing use of health services and development of new medication, the use of prescription drugs is increasing among the elderly[14]. From a clinical perspective, we discussed prescription changes as a risk factor for medication-related hospital admission. A nurse put it into the words: *'When they start to fiddle around with changing medication prescriptions you can wait for the hospitalisation that often follows'*. Several authors stated that nurses play an important role in patient medication safety. [15-19] When the course of a disease is changing, changes in medication prescriptions like dosage changes, stops, switches, or starts are more likely to occur. Except the study of Koecheler[20], who established in 1989 'medication regimen changes in 4 or more times during the past 12 months' as one of the 6 prognostic indicators for the selection of ambulatory patients who warrant pharmacist monitoring, to the best of our knowledge no other studies has been

carried out to evaluate the association between the number of prescription changes and hospital admission. Therefore, we were interested in determining whether the intensity of prescription changes is associated with hospital admissions and, if so, whether the strength of this association changes during the months before hospital admission.

The Chronic Disease Score (CDS) is an instrument that has shown to be clearly associated with the probability of hospitalisation. This CDS, developed in 1992, measures co-morbidity based on a one-year pharmacy dispensing data for seventeen therapeutic groups of somatic medications intended for chronic use. [21]

Aims and objectives

Anticipating whether the intensity of prescription changes (PCI) could be an additional independent warning signal to the established HARM study risk factors of hospital admission, the aim of this study was to assess the association between PCI and hospital admission in several time windows and to compare the PCI with the CDS.

Methods

Design

A retrospective, matched case-control study was performed.

Database

The study was conducted using data from the PHARMO Record Linkage System (RLS)(www.pharmo.nl). The PHARMO RLS includes pharmacy dispensing records from community pharmacies linked to hospital discharge records. It consists of a representative sample of more than 200 pharmacies in more than 50 regions scattered over The Netherlands and is representative for The Netherlands. Currently, it covers data of more than 2 million residents (12% of the Dutch population) regardless of insurance type. The computerized drug histories contain information concerning the dispensed drug, dispensing date, physician, amount dispensed and prescribed dosage regimen. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system. Patient information includes sex and date of birth. Each patient is

registered with an anonymous unique patient identification code that allows for observation of patient's drug therapy over time. The database does not provide information concerning the indication for use of the medicines or the complete registration of non-prescription products, as individuals may also purchase over-the-counter medication from non-pharmacy outlets.

Patients

Initially, 10,000 patients who had been hospitalised between July 1998 and June 2000 were randomly selected from the PHARMO RLS. The date of hospital admission was termed the index date. For each hospitalised patient, one control patient who was not admitted to a hospital, was matched by age, sex and geographic area, and assigned the same index date as the corresponding hospitalised patient. Patients were included in this study if medication data for a time window of at least 24 months before the index date were available.

Measurements

Prescription Change Intensity (PCI) was defined as the number of prescription changes during a 3-month time window. 4 different types of prescription changes were distinguished: (1) change in dosage, (2a) product switch, (2b) generic brand switch, (2c) therapeutic switch, (3) stop and (4) start (Table 1). We were interested in whether the effect of the PCI on hospitalisation changes over time. Therefore, we calculated the number of prescription changes during several 3-month time periods starting 18, 12, 9, 6, and 3 months before the index date. The duration of use of each drug was estimated by dividing the number of dispensed units by the prescribed daily dose instruction. Drugs that had a theoretical end date beyond 18, 12, 9, 6, or 3 months before the index date were considered as in use on these dates. Only drugs intended for systemic use were taken into account. Based on the distribution of the number of patients with prescription changes, the PCI was categorised by patient level into 0 prescription changes (PCI 0), 1 prescription change (PCI 1), 2 or 3 prescription changes (PCI 2 or 3) and ≥ 4 prescription changes (PCI≥ 4). We assessed PCI for the hospitalised as well as for the non-hospitalised group.

The Chronic Disease Score (CDS) is based on the use of pharmacy dispensing data of chronic medication over a one-year's time period. For seventeen somatic chronic diseases, scoring rules are attributed to corresponding medication classes. The CDS has shown to be a valid measure of complications related to an

individual patient's burden of somatic chronic diseases and is clearly associated with the probability of being hospitalised based. [22,23 24] To compare the PCI to the CDS, the CDS was measured for the year preceding the index date. Based on the distribution of the CDS scores, the CDS score was categorised into 4 categories: CDS score = 0, CDS score = 1 or 2, CDS score = 3 or 4 and CDS score ≥5.

Table 1. Classification of Prescription Changes

Classification	Definition
1. Change in dosage	Change in dosage means that, for the same drug, the daily dosage is increased or decreased (e.g., amitriptyline 25 mg changes in amitryptyline 10 mg or vv).
2a. Product switch	Change to a drug containing the same active substance but in a different formulation (e.g.,metoprolol 50 mg plain tablet instead of metoprolol slow release tablet (Selokeen ZOC®)).
2b. Generic brand switch	Change to another product containing the same active substance with the same strength and the same dosage (e.g., atenolol 50 mg tablet (generic product) instead of Tenormin® 50 mg tablet (brand) or Renitec® 10 mg tablet (brand) instead of enalapril 10 mg tablet).
2c. Therapeutic switch	Change to another active substance within the same therapeutic group; the first 4 characters of the ATC classification are the same (e.g. amitriptyline (N06AA09) instead of citalopram (N06AB04) or fluoxetine (N06AB03) instead of citalopram (N06AB04)).
3. Stop	No continuation 90 days after one of the five control time points and no generic-brand substitution (1), product formulation switch (2) or therapeutic switch (3).
4. Start	Start of a drug means prescription of a drug which had not been prescribed during the previous 6 months and which is not a generic brand substitution (1), product formulation switch (2) or therapeutic switch (3).

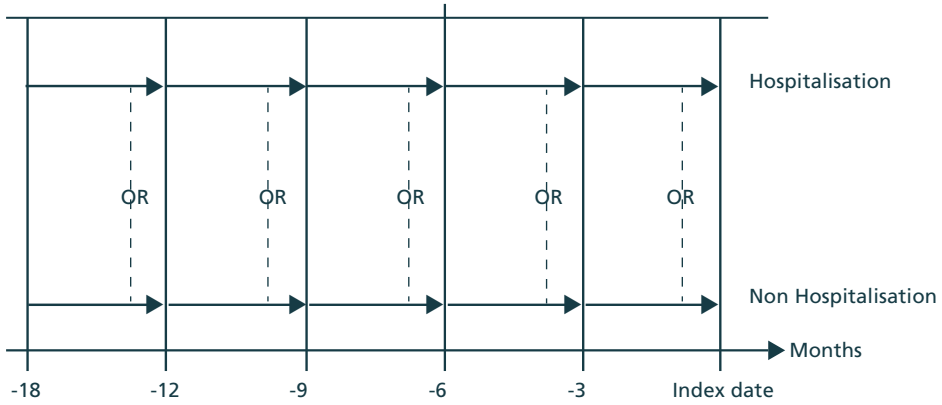


Figure 1. **Prescription Change Intensity for hospitalised and nonhospitalised patients at 18, 12, 9, 6 and 3 months before index date**

Statistical analysis

The number of prescription changes was calculated for each patient in the hospitalised and non-hospitalised group during five different time windows as shown in Figure 1. The strength of the association between prescription change intensity and hospital admission was calculated by comparing the number of patients in each prescription changes category in the hospitalised and non-hospitalised group at 18, 12, 9, 6 and 3 months before the index date and was expressed as the Odds Ratio (95%CI). The no prescription changes group (PCI cat 0) was taken as the reference group.

To assess the effects of other factors associated with patient and hospitalisation characteristics, stratified analyses were done on age (< 65 years ≥ 65 years), admission type (emergency or planned), CDS score, and polypharmacy (the use of five or more drugs concomitantly).

To assess the strength of the association between the CDS score and hospital admission, the number of patients per CDS category for hospitalised and non-hospitalised patients was compared and expressed as the Odds Ratio (95%CI). The CDS score 0 was taken as the reference group. The nature of prescription changes was calculated for each of all different time periods. The correlation between the PCI and CDS was measured with a two-tailed Spearman's correlation coefficient. Statistical analyses were performed using SPSS 16.0 (SPSS, Chicago, IL).

Results

The source population was comprised of a random sample of 10,000 patients admitted to a hospital and an equal number of matched non-admitted persons. Because 1,319 matched patients had less than 24 months of exposure history available in PHARMO RLS, the final study population comprised 8,681 case patients- and 8,681 control patients. The characteristics of the study population are displayed in Table 2. The mean age was 52.6 years (SD 21.8) and 58.7% of the patients were female. At the index date, 60.6% of the patients in the hospitalised group and 47.8% of the patients in the non-hospitalised group were using any type of medication for systemic use. The mean number of drugs being used at the index date by cases and controls was 3.0 and 2.1 drugs, respectively. In both groups the number of drugs taken increased with age. The CDS was higher in the hospitalised group than in the non-hospitalised group. The most frequent prescription changes at 3 months before the index date were stops (hospitalised 58.6% vs. 64.2% non-hospitalised) and changes in dosage (22.6% vs. 20.5%); other prescription changes varied in the range of 3-6%.

Risk of hospital admission based on PCI and CDS score

The risk of hospital admission increased with the number of prescription changes. The odds ratio between hospitalised and non-hospitalised patients per PCI category at 3 months before the index date increased as the PCI category increased 1.4 [95% CI 1.3-1.5] in the lowest PCI category and 4.1 [95%CI 3.1-5.1] in the highest (Figure 2). Besides 3 months before the index date the odds ratio per PCI category increased also at 18, 12, 9 and 6 months before index date (Table 3).

The risk of hospital admission based on CDS score also increased per CDS category. A higher CDS score was associated with an increased risk of hospitalisation (CDS= 1-2 OR 1.5 [95% CI 1.4-1.6], CDS=3-4 OR 1.7 [95%CI 1.6-1.9] and CDS ≥5 OR 3.6 [95%CI 3.3-3.9]).

Stratification by age category (< 65 years ≥ 65 years), admission type (planned or emergency admission), CDS score and polypharmacy showed comparable increases in odds ratios with increasing numbers of prescriptions changes. For polypharmacy patients, the odds ratio of PCI ≥ 4 decreased between nine months and 3 months before the index date from 3.5 [95%CI 1.9-6.67] to 2.2 [95%CI 1.0-5.4]. Stratification by CDS score demonstrated increasing

odds ratios between hospitalised and non-hospitalised patients by prescription change intensity (Figure 3).

Table 2. Characteristics of Hospitalised and Non-Hospitalised Patients at the Index date

Characteristics		Hospitalised	%	Non-Hospitalised	%
		N=8681		N=8681	
Sex					
	Male	3588	41.3	3588	41.3
	Female	5093	58.7	5093	58.7
Age (years at index date)					
	0 - ≥ 18	574	6.6	574	6.6
	>18 - ≥ 45	2737	31.5	2737	31.5
	> 45 - ≥ 65	2246	25.9	2246	25.9
	> 65 - ≥ 79	2218	25.6	2218	25.6
	> 79	906	10.4	906	10.4
Number of medications					
	0	3416	39.4	4534	52.2
	1	1794	20.7	2121	24.4
	2	985	11.3	872	10.0
	3	767	8.8	535	6.2
	4	544	6.3	302	3.5
	≥5	1175	13.5	317	3.7
CDS category					
	CDS score 0	3671	42.3	5206	60.0
	CDS score 1-2	1331	15.3	1287	14.3
	CDS score 3-4	1731	19.9	1415	16.3
	CDS score ≥5	1948	22.4	773	8.9
Duration of hospitalisation					
	1 day	417	4.8		
	2-5 days	4374	50.4		
	> 5days	3890	44.8		
Admission type					
	Emergency	3966	45.7		
	Planned	4715	54.3		
Admission for surgery					
	Yes	4360	50.2		
	No	4321	49.8		

Comparison PCI and CDS score

A two-tailed Spearmans' correlation coefficient showed a significant but poor correlation at 3 months before index date between CDS 0 and PCI 0 (0.019, p-value 0.01) and CDS ≥5 and PCI ≥4 (0.027, p-value 0.01) and no significant correlation between CDS 1 or 2 and PCI 1 and CDS 3 or 4 and PCI 2 or 3.

Table 3. Association between Hospitalised (N=8681) and Non-Hospitalised (N=8681) Patients per PCI Category at Different Time Points before Index date

	-18 Months			-12 Months			-9 Months			-6 Months			-3 Months		
	H%	NH%	OR(95% CI)	H%	NH%	OR(95% CI)	H%	NH%	OR(95% CI)	H%	NH%	OR(95% CI)	H%	NH%	OR(95% CI)
PCI cat															
0	70.1	77.6	1(ref)	67.3	75.2	1(ref)	66.7	75.5	1(ref)	65.9	75.7	1(ref)	64.4	75.3	1(ref)
1	18.8	16.3	1.3(1.2-1.4)	19.9	18.2	1.2(1.2-1.3)	19.8	18.0	1.3(1.2-1.4)	20.2	17.1	1.4(1.3-1.5)	20.1	17.2	1.4(1.3-1.5)
2 or 3	8.8	5.2	1.9(1.7-2.1)	9.8	5.9	1.9(1.7-2.1)	10.4	5.6	2.1(1.9-2.3)	10.6	6.2	2.0(1.8-2.2)	11.9	6.5	2.2(1.9-2.4)
≥4	2.3	0.9	3.0(2.3-3.4)	2.9	0.9	3.6(2.8-4.6)	3.2	0.9	4.2(3.3-5.4)	3.3	1.0	3.8(3.0-4.8)	3.6	1.0	4.1(3.1-5.1)

Abbreviations: H = Hospitalised patients, NH = Non-Hospitalised, Ref = Reference,
PCI cat = Prescription Change Intensity Category.

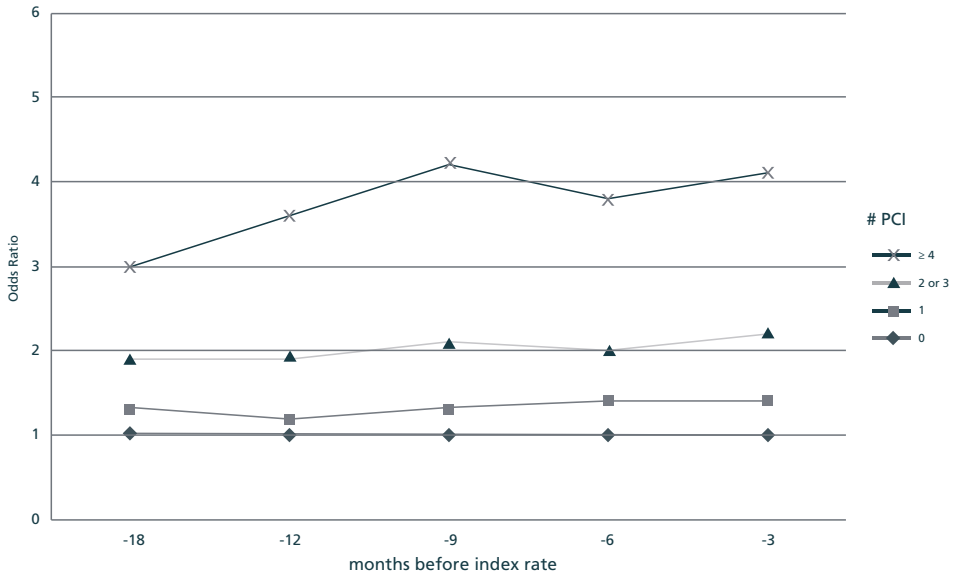


Figure 2. **Risk for hospital admission**

Discussion

The main finding of this study is that intensity of prescription changes (PCI) is associated with increased risk of hospital admission. We also confirmed the known association of the Chronic Disease Score (CDS) with hospital admission. The PCI and CDS are both associated with hospital admission based on pharmacy records. However, the correlation between PCI and CDS categories in this study was poor. Consequently, the PCI cannot replace the CDS. We found that among patients with a low CDS score an increasing number of prescription changes was associated with an increased risk of hospital admission. Stratified analysis of the CDS scores into the 4 categories confirmed this finding: at each CDS category, we found a comparable increase in the odds ratio on risk of hospitalisation caused by the number of prescription changes.

Stratification by age category (<65 or ≥65 year) and medication use (< 5 or ≥5 drug taken) showed increasing odds ratios per PCI in both strata, as presented in figure 2. Several studies showed age and polypharmacy as a risk factor for hospital admission. In the study under investigation, even patients younger than

65 years old and patients without polypharmacy showed increasing risk for hospital admission based on the PCI. It is plausible that planned admissions have a lower risk for hospital admission than acute admissions. Therefore, we stratified on admission type. This stratification could not confirm this assumption. Of interest are the findings that polypharmacy patients showed a decreased risk of hospital admission. PCI ≥4 decreased between 9 and 3 months before the index date (Figure 3). Based on this finding, it can be stated that the most frequent prescription change, 'stop,' has a protective effect for hospital admission for polypharmacy patients.

The CDS has the disadvantage of requiring the availability of medication history information for at least one year prior to the event under investigation. In this study, the possibility of predicting hospital admission based on the number of prescription changes in a 3-month period was demonstrated. On the other hand, for calculating the CDS, only a summary of chronic drug use needs to be available; for calculating the PCI, detailed medication histories are required. The CDS was developed to measure a patient's overall health status. The PCI is not suited for this objective. The CDS was developed in 1992 and was never adjusted for the introduction of new medication classes. Notwithstanding this limitation, the CDS is still associated with hospital admissions. Because the PCI is based on the number of changes of all prescribed drugs, new medications are also taken into account.

To appreciate the present results, a number of aspects need to be discussed in perspective of the scope and limitations of this study. First, the database does not provide information concerning the indication of use. Second, complete registration of non-prescription medicines is lacking as patients may also purchase these drugs from non-pharmacy outlets (OTC). Another relevant aspect is that prescribers may fail to write a prescription for each change in drug use; for identifying prescription changes, only dispensing data of the community pharmacies were used. Therefore, the association between PCI and hospital admission could have been underestimated. Furthermore, the data set that was used in this study covered a time period between July 1998 and June 2000. Although unlikely, it is possible that during the past ten years, the prescribing behaviour of general practitioners could have been influenced by medication reconciliation programs. Besides from the perspective of cuts and innovation, indications for hospital admission could have become stricter over ten years. Subsequently, this could lead to an overestimation of the results.

No data was available concerning the social economic status of the patients in the study and issues with respect to compliance to therapy could not be taken into account. It can be that subjects in the control group were less sick than the group of hospitalised patients. However, as controls were sampled independently of exposure status, this difference in health status will not influence our results. To our knowledge, besides the study of Koecheler *et al.* no other studies have considered the subject of prescription changes and risk of hospital admission. Several other studies, like the HARM study, have described risk factors for medication-related hospital admission, but did not focus on changes in prescriptions.

Conclusions

This study provides results based on a longitudinal study of a large group of patients over a period of 24 months. It demonstrates, for the first time, the association between the intensity of prescription changes (PCI) and hospital admission within a 3-month period. The PCI is an alternative measurement for predicting hospital admission.

Relevance to clinical practice

In the ambulant setting the PCI score could function as a warning signal for increased hospitalisation risk and to contribute to medication safety programs. Especially older patients who use more medication in general are likely to benefit this PCI score. District nurses and social workers in primary care should be alerted when the intensity of prescription changes increases for their patients. Pharmacists in primary care can use the PCI as a clinical rule for early recognition of potential drug related problems. Further research is recommended to determine the predictive value of the PCI in practice as a clinical rule.

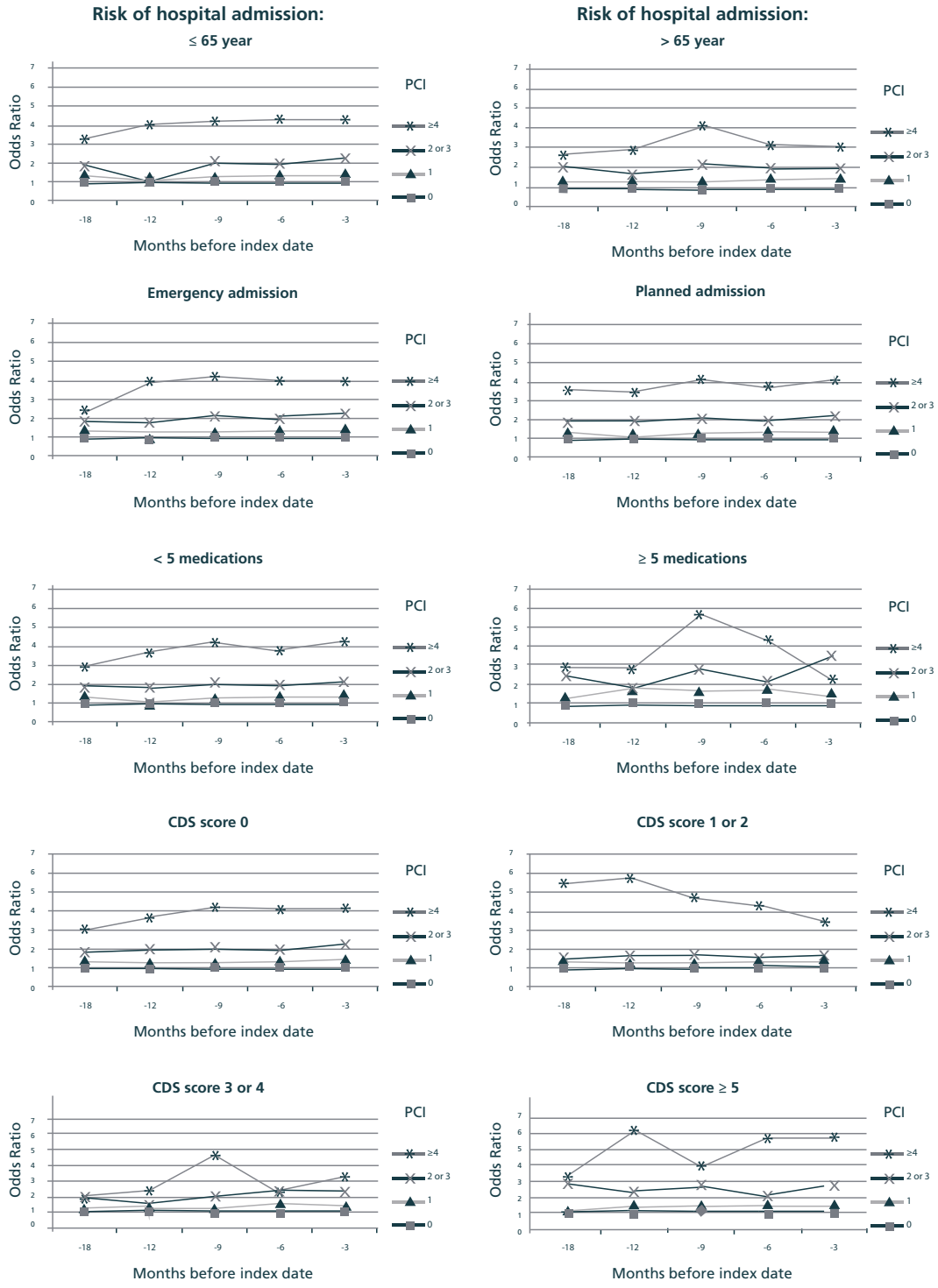


Figure 3. Stratification on age, admission type, < or ≥ 5 medications and CDS score

References

1. Lazarou, J., Pomeranz, B. H., & Corey, P. N., "Incidence of adverse drug reactions in hospitalised patients: a meta-analysis of prospective studies", Journal of the American Medical Association, 1998, vol. 279, no. 15, pp. 1200-5
2. Green, C. F., Mottram, D. R., Rowe, P. H., & Pirmohamed, M. , "Adverse drug reactions as a cause of admission to an acute medical assessment unit: a pilot study", Journal of Clinical Pharmacy and Therapeutics, 2000, vol. 25, no. 5, pp. 355-61
3. Roughead, E. E., Gilbert, A. L., Primrose, J. G., & Sansom, L. N. "Drug-related hospital admissions: a review of Australian studies published 1988-1996", The Medical Journal of Australia, 1998, vol. 168, no. 8, pp. 405-8
4. Pouyanne, P., Haramburu, F., Imbs, J. L., & Begaud, B. , "Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. French Pharmacovigilance Centres", British Medical Journal, 2000, vol. 320, no. 7241, p. 1036
5. Beijer, H. J. & de Blaey, C. J. "Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies", Pharmacy World Science, 2002, vol. 24, no. 2, pp. 46-54
6. Onder, G., Pedone, C., Landi, F., Cesari, M., Della,V. C., Bernabei, R., & Gambassi, G. "Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA)", Journal American Geriatric Society, 2002, vol. 50, no. 12, pp. 1962-8
7. Waller, P., Shaw, M., Ho, D., Shakir, S., & Ebrahim, S. "Hospital admissions for 'drug-induced' disorders in England: a study using the Hospital Episodes Statistics (HES) database", British Journal of Clinical Pharmacology, 2005
8. Klarin, I., Wimo, A., & Fastbom, J. "The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old", Drugs Aging, 2005, vol. 22, no. 1, pp. 69-82
9. Van der Hooft, C. S., Sturkenboom, M. C., van Grootheest, K., Kingma, H. J. & Stricker, B. H. 'Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands', Drug Safety, 2006, vol. 29, no. 2, pp. 161-8
10. Kongkaew, C., Noyce, P. R., & Ashcroft, D. M. "Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies", Annals of Pharmacotherapy, 2008, vol. 42, no. 7, pp. 1017-25

11. Leendertse, A. J., Egberts, A. C., Stoker, L. J., & van den Bemt, P. M. "Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands", Archives of Internal Medicine, 2008, vol. 168, no. 17, pp. 1890-6
12. Bulechek, G.M., McCloskey, J.C. & Mc Closkey-Dochterman, Co. Nursing interventions; essential nursing treatments. W.B. Saunders Co: Philadelphia, 1992, pp. 213
13. Higashi, T., Shekelle, P. G., Solomon, D. H., Knight, E. L., Roth, C., Chang, J. T., Kamberg, C. J., MacLean, C. H., Young, R. T., Adams, J., Reuben, D. B., Avorn, J., & Wenger, N. S. "The quality of pharmacologic care for vulnerable older patients", Annals of Internal Medicine, 2004, vol. 140, no. 9, pp. 714-20
14. Linjakumpu, T., Hartikainen, S., Klaukka, T., Veijola, J., Kivela, S. L., & Isoaho, R. "Use of medications and polypharmacy are increasing among the elderly", Journal of Clinical Epidemiology, 2002, vol. 55, no. 8, pp. 809-17
15. Arnold, G. J. Clinical recognition of adverse drug reactions: obstacles and opportunities for the nursing profession, Journal of Nursing Care Quality, 1998, vol. 13, no. 2, pp. 45-55
16. Ndosi, M. E. & Newell, R. "Nurses' knowledge of pharmacology behind drugs they commonly administer", Journal of Clinical Nursing, 2009, vol. 18, no. 4, pp. 570-580
17. Bergqvist, M., Ulfvarson, J., & Karlsson, E. A. "Nurse-led medication reviews and the quality of drug treatment of elderly hospitalised patients", European Journal of Clinical Pharmacology, 2009, vol. 65, no. 11, pp. 1089-96
18. Lucero, R. J., Lake, E. T., & Aiken, L. H. "Nursing care quality and adverse events in US hospitals", Journal of Clinical Nursing, 2010, vol. 19, no. 15-16, pp. 2185-95
19. Sulosaari, V., Suhonen, R., & Leino-Kilpi, H. "An integrative review of the literature on registered nurses' medication competence", Journal of Clinical Nursing, 2011, vol. 20, no. 3-4, pp. 464-78
20. Koecheler, J. A., Abramowitz, P. W., Swim, S. E., & Daniels, C. E. "Indicators for the selection of ambulatory patients who warrant pharmacist monitoring", American Journal of Health-System Pharmacy, 1989, vol. 46, no. 4, pp. 729-32
21. Von Korff, M., Wagner, E. H., & Saunders, K. 'A chronic disease score from automated pharmacy data', Journal of Clinical Epidemiology, 1992, vol. 45, no. 2, pp. 197-203
22. Clark, D. O., Von, K. M., Saunders, K., Baluch, W. M., & Simon, G. E. "A chronic disease score with empirically derived weights", Medical Care, 1995, vol. 33, no. 8, pp. 783-95

23. Fishman, P. A. & Shay, D. K. "Development and estimation of a pediatric chronic disease score using automated pharmacy data", Medical Care, 1999, vol. 37, no. 9, pp. 874-83
24. Putnam, K. G., Buist, D. S., Fishman, P., Andrade, S. E., Boles, M., Chase, G. A., Goodman, M. J., Gurwitz, J. H., Platt, R., Raebel, M. A., & Arnold, C. K. "Chronic disease score as a predictor of hospitalisation", Epidemiology, 2002, vol. 13, no. 3, pp. 340-6

Chapter 3.2

THE MEASUREMENT OF ANTICHOLINERGIC DRUG LOAD AND ITS ASSOCIATION WITH THE OCCURRENCE OF DELIRIUM IN ELDERLY ORTHOPAEDIC SURGERY PATIENTS

Rutger Stuffken
Madelon H. Butterhoff-Terlingen
Ralph Vreeswijk
Eibert R. Heerdink
Marieke C.H. Kerskes
Rob J. van Marum
Carolien van Rees
Toine C.G. Egberts
Kees J. Kalisvaart

Abstract

Objective

To compare various instruments for the assessment of anticholinergic (ACH) drug load and to assess the association of ACH drug load with the occurrence of delirium in a cohort of orthopaedic surgery patients.

Participants

Three hundred ninety-seven patients admitted for acute or elective hip surgery who participated in a previous trial to study the effectiveness of haloperidol prophylaxis in patients at risk for delirium.

Measurements

Each drug used at admission was assigned an ACH score, using 6 different instruments. The patients were prospectively screened for the occurrence of delirium after surgery and the association between the ACH drug load and the occurrence of delirium was assessed.

Results

The study population consisted of 397 patients and the number of different drugs used was 185. Each of the 6 instruments compiles a different number of drugs classified with any ACH load. The prevalence of patients with any ACH drug load varied largely between the 6 evaluated instruments (9% to 80%). Delirium occurred in 68 (17.1%) patients. Regardless of the instrument used, the ACH drug load did not show a significant association with the occurrence of delirium (adjusted odds ratio between 0.65 [95% CI = 0.36-1.16] and 1.30 [95% CI = 0.54-3.15]).

Conclusion

No single instrument can be used as an independent guide for quantifying ACH drug load. In addition, it is unclear if ACH drug load is a risk factor for delirium and further studies are necessary to assess this relationship.

Introduction

Delirium is a serious but partly preventable psychiatric disorder that frequently occurs in hospitalised elderly patients. It is characterized by an acute onset of disturbance of consciousness or disorganized thinking.[1,2] The incidence is highly variable and has been estimated between 5-52% during hospitalisation.[3,4] The wide variability is due to the diagnostic criteria applied and the differences in the population studied. Delirium occurs especially postoperatively and in intensive care patients.[5,6] It is associated with longer hospital stay, poor recovery, institutionalization following hospital discharge and high morbidity and mortality.[7,8,9] Many factors are believed to be responsible for the development of delirium. Previous studies indicate that at least 30-40% of cases may be preventable.[10] One of the modifiable risk factors to prevent delirium is medication. Although results are not consistent, many publications have shown that the use of medications with anticholinergic properties is associated with delirium more commonly than any other drug class.[11,12,13] The use of anticholinergic (ACH) drugs is more common in older individuals who are also more sensitive to their effects. In addition, the elderly frequently use over-the-counter medication like antihistamines and anti-ulcer drugs which may contribute to the ACH drug load.[14,15] Based on a radioreceptor assay, Tune *et al* found that 10 of the 25 most commonly prescribed drugs for older adults posses anticholinergic effects and are associated with impairments in memory and attention.[16] Several measurement scales have been developed to quantify ACH drug load of medication and these methods are all based on different properties with different interpretations and results.[17,18] To date there is no accepted universal method or rating scale.

The objective of this study was to compare different instruments for the assessment of ACH drug load as well as to assess the association of the aggregate ACH drug load with the occurrence of delirium in a cohort of elderly orthopaedic surgery patients.

Methods

Setting and Study Population

For the present study data were used that were collected from a previous study published by Kalisvaart et al.[19] In brief that study was a randomized, double-blind, placebo-controlled trial to evaluate the effectiveness of haloperidol prophylaxis on the incidence, severity and duration of postoperative delirium in elderly hip-surgery patients at risk for delirium. The study was conducted in a 915-bed teaching hospital in Alkmaar, the Netherlands, between August 2000 and August 2002. Patients aged 70 years or older were recruited and were eligible if they did not have any of the following conditions: delirium at admission, a lack of risk factors for post-operative delirium present at baseline, use of cholinesterase inhibitors, parkinsonism, epilepsy, levodopa treatment, inability to participate in interviews (because of profound dementia, language barrier, intubation, respiratory isolation, aphasia, coma or terminal illness), a delay of surgery of more than 72 hours after admission or a prolonged QTc-interval. The baseline screening and assessments were completed within 12 hours of admission and before surgery. Risk classification was based on the presence of one or more predictive risk factors as described by Inouye *et al.* [20]: visual impairment, defined as binocular near vision worse than 20/70 after correction, severe illness measured by the Apache II (Acute Physiology Age and Chronic Health Examination, scale 0 to 70),with a cut-off score of > 16 indicating increased severity [21], cognitive impairment measured with the Mini Mental Status Examination (MMSE) score of < 24 on a scale of 0 to 30 and dehydration (ratio of blood urea nitrogen to creatinine of ≥ 18).[22] Medication use at the time of admission was assessed by the patient's medical record and was verified on admission. The members of the research team that were not involved in the clinical care of the patients carried out all baseline and outcome assessments. The assessors had extensive training prior to the study and followed standard procedures. All data were collected on standardized patient record forms and the data underwent extensive checks for errors and validity.

In conclusion in this study low-dose haloperidol prophylactic treatment demonstrated no efficacy in reducing the incidence of post-operative delirium. It only did have a positive effect on the severity and duration of delirium.

Measurement of Anticholinergic Drug Load

ACH load was quantified for each patient by assigning an ACH score to each of the drugs used by the patients. These scores were based on an extensive review of the literature using the PubMed databases from 1990 -2007 with ACH load and drug use as the main research criteria. We selected two different instruments for assigning the ACH score based on a receptor binding study and one instrument based on drug characteristics and clinical experience. In addition, we added the use of the data-base of the Scientific Institute of Dutch Pharmacies (WINAp), the EMEA Summary of Product Characteristics and a consensus rating of an expert panel as extra instruments in our study. The characteristics of those 6 instruments are summarized in Table 1.

1. Tune [15,23]
   ACH activity was based on the results of a receptor binding study. The ACH effects of 25 drugs at a standard concentration of 10^{-8} M were expressed as atropine equivalents. Drugs with an ACH activity of 0-0.2 ng/ml atropine equivalents were rated with a score of +1, and drugs with an ACH activity of ≥ 0.2 ng/ml atropine equivalents were rated with a score of +2. Those drugs used in our study that showed either no ACH activity or were not classified were assigned a score 0.
2. Carnahan [24,25]
   ACH activity was based on published receptor binding studies. For a list of 340 drugs the ACH effect of each drug was rated from a score 0 (no known ACH activity) to a score of +3 (marked ACH activity). The drugs used in our study that were not classified in this instrument were assigned a score of 0.
3. Summers [26]
   A list of 67 psychoactive drugs was divided into 4 classes: class I (score of +1) included drugs that have known synergistic effects with ACH agents, but not cause acute organic mental syndrome; class II (score of +2) included drugs that are known to cause delirium but not documented to have CNS ACH properties and class III (score of +3) included drugs that have central nervous system ACH effect cause delirium. The drugs in our study that showed no ACH activity or were not classified were assigned a score of 0.

Table 1. Characteristics of 6 Instruments Used to Assess Anticholinergic Drug Load

Instrument	Anticholinergic (ACH) Score	Remarks
1. Tune	0: 0 ng/ml atropine equivalents 1: 0-0,2 ng/ml atropine equivalents 2: ≥ 0,2 ng/ml atropine equivalents	Scores are based on receptor binding study. ACH effects of 25 drugs at a standard concentration of 10-8 M based on a radio- receptor assay and expressed as atropine equivalents
2. Carnahan	0: no known ACH properties 1: posible ACH properties 2: intermediate ACH properties 3: markedly ACH properties	ACH properties were based on data from receptor binding studies
3. Summers	0: no known ACH properties 1: known synergistic effect with ACH agents, not known as a direct cause of acute mental syndrome 2: known to cause delirium, no documented ACH properties. 3. known to cause delirium and known ACH properties.	Scores are based on drug characteristics and clinical experience. This study measured the ACH effects of 67 psychoactive drugs
4. Scientific Institute of Dutch Pharmacies (WINAp)	0: no known ACH properties 1: well known ACH properties	Scores are a dichotomous classification based on drug characteristics and assessed by an expert panel
5. Expert panel	0: no known ACH properties 1: intermediate ACH properties 2: markedly ACH properties	Based on clinical experience The expert panel consisted of 2 clinical geriatrics, 3 hospital pharmacists and 1 fellow hospital pharmacist conducting an independent rating based on clinical experience
6. Summary of Product Characteristics	0: no ACH side effect 1: 1 ACH side effect 2: 2 ACH side effects 3: 3 ACH side effects	Scores wee based on drug characteristics. Product characteristics of all drugs involved were screened for urinary retention, visual acuity and dry mouth

4. Scientific Institute of Dutch Pharmacies (WINAp)
   The Scientific Institute of Dutch Pharmaciess (WINAp) provides a database of all drugs available in the Netherlands. This database includes all known adverse reactions of these drugs. Drugs involved in this study were separated into a dichotomous classification. No known ACH properties (score 0) or well known ACH activity (score +1). Those drugs used in our study that were not classified were assigned a score of 0.
5. Expert panel
   The expert panel included two geriatric physicians, 3 hospital pharmacists and 1 fellow hospital pharmacist. All drugs involved in this study were classified by the clinical experience of the panel members. They ranked the identified medications by consensus with a score of 0 (no ACH activity), +1 (intermediate ACH activity) or +2 (marked ACH effects).
6. Summary of Product Characteristics (SPCs). The number of ACH side effects described in the EMEA summary product characteristics were used to classify all drugs used in this study. The product characteristics were screened for urinary retention, visual acuity and dry mouth. Drugs were classified as having one ACH side effect (score +1), two ACH side effects (score +2) or 3 ACH side effects (score +3). Those drugs used in our study that showed either no ACH activity or were not classified were assigned a score of 0.

Outcomes

The occurrence of postoperative delirium was defined as delirium occurrence within a period of five postoperative days. Diagnosis of the syndrome was defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) edition IV [27] and the Confusion Assessment Method criteria (CAM).[28,29]

Table 2. Baseline Characteristics of the Patients upon Admission

	Delirium (n=68)	No-delirium (n=329)	p-value
Age, mean ± SD	82.43 (± 6.50)	78.53 (± 5.88)	0.04
Female, n (%)	47 (69,1%)	271 (82,3%)	
MMSE, mean ± SD⋆	21.13 (± 4.41)	25.33 (± 3.98)	0.085
Visual acuity mean ± SD#	0.34 (± 0.14)	0.41 (± 0.16)	0.09
APACHE-II, mean ± SD §	15.13 (± 3.71)	13.04 (± 2.93)	0.002
Creatinine/urea ratio ± SD†	11.92 (± 3.89)	11.71 (± 3.48)	0.061
Number of drugs used at the admission date, mean ± SD	3.74 (±3.17)	3.34 (± 2.57)	0.095
Number of drugs used at the admission date, range	0-15	0-11	
Baseline vulnerability ± SD	2.18 (± 0,91)	1.50 (± 0.76)	0.05

⋆ Range 0 (severe cognitive impairment) to 30 (no cognitive impairment)

Range 20/20 (no visual impairment) to 20/800 (severe visual impairment)

§ Range 0 (no acute health problems) to 70 (severe acute health problems)

† Ratio over 18 indicates dehydration

Data Analyses

For each patient, the ACH drug load from medications was quantified by summing the scores of the 6 instruments (i.e., 3 drugs with a rating scale of 1 would be equally to one drug with a score of 3). The association between the ACH drug load and the occurrence of delirium was assessed using logistic regression and was sequentially adjusted for the a priori selected covariates (APACHE II score, MMSE score, visual acuity and creatinine/urea ratio). Statistical evaluation was performed using SPSS for Windows, version 16.0 (SPSS Inc Chicago, IL).

Ethical Considerations

The study was undertaken in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. Approval of the regional research ethics committee was obtained. All patients or their relatives gave fully informed written consent.

Results

Measurement of the Anticholinergic Drug Load

The study population comprised 603 patients, but 206 patients had to be excluded because of a lack of information about their medications. Therefore, the final population consisted of 397 patients, in whom delirium occurred in 68 (17.1%) patients. The characteristics of the patients are presented in Table 2. Individuals in the delirium group had a lower, but not significant MMSE score indicating poorer cognitive functioning as well as poorer visual acuity scores and a higher Apache-II scores ($p=0.002$). Upon admission, the 397 patients were using a total of 185 different drugs (range delirium 0-15 and no delirium 0-11). The drugs were categorized using the 6 different instruments in order to assign the ACH load. Each of the 6 instruments compiles a different number of drugs classified with any ACH load. Classification of any level of ACH drug load occurred in the range of 9-80% of all different drugs for the 6 instruments (Figure 1). The Summary Product Characteristics and the expert panel showed a classification for all 185 drugs. Table 3 shows those drugs with the highest ACH score classified by at least one of the 6 different instruments. In this study, there was no drug with an ACH score for all 6 instruments.

Assessment of the Association with Delirium

For each instrument the strength of the association between the anticholinergic drug load and the occurrence of delirium was calculated and expressed as an odds ratio (Figure 2). We found no association for any of the instruments (adjusted odds ratio between 0.65 [95% CI = 0.36-1.16] and 1.30 [95% CI = 0.54-3.15].

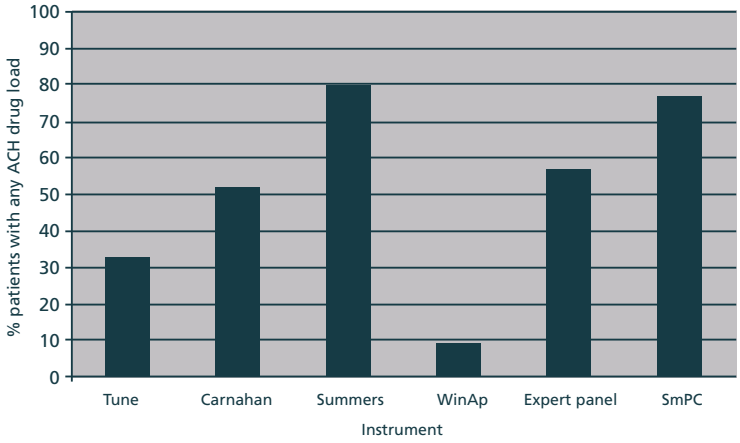


Figure 1. The relationship between the instrument and the number of patients with any ACH drug load

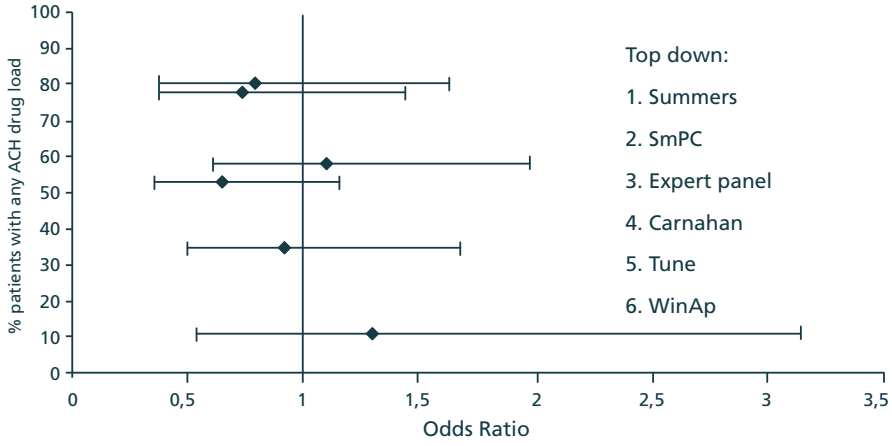


Figure 2. The relationship between the prevalence of patients with any ACH drug load and the adjusted odds ratios for the association between the occurrence of delirium and the number of patients with ACH drug load

Discussion

We used 6 different instruments to quantify ACH drug load in our cohort of older orthopaedic surgery patients and observed a significant variation in the prevalence of drugs with an ACH drug load. All of the 6 instruments classified different number of drugs as having any ACH activity. The method of the expert panel and the EMEA Summary of Product Characteristics compiled

a classification for all 185 drugs. There were large discrepancies between the 6 instruments in classifying drugs into 'none', 'low', 'intermediate' or 'high' scores for ACH load. Furthermore we found no association of the classification of ACH drug load between the instruments when they were based solely on receptor binding properties or based on clinical experience or based on drug characteristics. So we can conclude that there is no universal classification for quantifying ACH load due to the use of drugs.

The method defined by Tune only classified 25 drugs by receptor binding capacity. The usefulness of this instrument is limited because multiple new drugs have entered the market since this study. Nevertheless this study was not to create a thorough instrument, but to examine a small subset of commonly used drugs for possible ACH effects, new research will regular be compared with the method by Tune. Recently Cox *et al.* discussed the idea that the role of ACH in disease states using the serum anticholinergic activity assay, should be re-evaluated.[30] Campbell *et al.* conducted a systematic evidence review that found for several studies an association between ACH use and worsening cognitive performance either through an acute (delirium) or chronic (mild cognitive impairment) impact.[31]

Table 3. Drugs with the Highest Rating Scale of ACH Load

Drug	Tune	Carnahan/ Han	Summers	Sc. Institute of Dutch Pharmacies (WINAp)	Expert-panel	SPCs
Furosemide	2	1	0	0	0	1
Prednisolone	2	1	2	0	0	0
Cimetidine	2	2	0	0	1	0
Ranitidine	2	2	0	0	1	1
Nifedipine	2	1	0	0	1	2
Digoxin	2	1	2	0	1	1
Phenobarbital	0	0	3	0	0	1
Diazepam	0	1	3	0	1	1
Flurazepam	0	1	3	0	1	1
Pimozide	0	2	0	0	2	1
Mannitol	0	0	0	0	0	3
Baclofen	0	0	0	0	1	3
Sertraline	0	1	0	0	1	3
Paroxetine	0	1	0	0	1	3
Tramadol	0	1	0	0	1	3
Clemastine	0	3	0	1	1	1
Ipratropium	0	0	0	1	1	3
Morfine	0	1	3	0	1	3
Carbamazepine	0	2	0	0	2	3
Hydroxyzine	0	3	2	1	2	1
Cinnarizine	0	0	0	1	2	3
Disopyramide	0	2	0	1	2	3
Thioridazine	0	3	3	1	2	0
Oxybutinin	0	3	0	1	2	3
Tolterodine	0	3	0	1	2	3
Promethazine	0	3	3	1	2	3
Amitriptyline	0	3	3	1	2	3
Doxepine	0	3	3	1	2	3
Nortriptyline	0	3	3	1	2	3

In our study we used the various instruments to assess the strength of the association between the total ACH drug load and the risk for the occurrence of delirium. There was no significant association regardless of what instrument was used. However, there was a twofold difference in strength of association, depending on the instrument used. This could explain the inconsistency of this association in literature. Even when we calculated the association between delirium and total ACH drug load using the score of the drugs with the highest rating scale, we did not observe an association. Although ACH mechanisms have received the most attention, it is unlikely that only one neurotransmitter system underlies all cases of delirium. Various neurotransmitter alterations, including dopamine, serotonin, GABA and glutamate may converge to result in a delirium syndrome.[32,33] Further study should be done to understand these neurotransmitter mechanisms in the aetiology of delirium.

One of the limitations of this study was that it was a single-site study. In addition, this study was slightly underpowered because of the relatively low delirium rates in both hip-fracture and elective hip surgery patients. The relatively low APACHE-scores indicates that the study group was in a relatively in good clinical condition overall. It remains to be seen whether our findings can be generalized to a normal population or a seriously ill population, such as intensive care patients. The analysis was adjusted for a relatively small number of covariates. We also adjusted for different age-groups and sex and found that age and sex was not a additional risk factor for the development of delirium. We did not take into account the nature of the surgical procedures and the post surgical sedation impact on delirium assessment. Because the study population was conducted in a single-site hospital, surgical procedures were standardized procedures and equal for each patient. Because of a lack of information about the doses and duration of actual medications, we didn't take this into account.

Conclusion

Delirium is a common outcome of seriously ill hospitalised patients. ACH activity has long been suggested to play a major role in development of postoperative delirium. In many studies, investigators have tried to show a relationship between the use of ACH drugs and the prevalence of delirium using different instruments to measure ACH drug load. In this study we compared 6 different instruments to establish the association between total

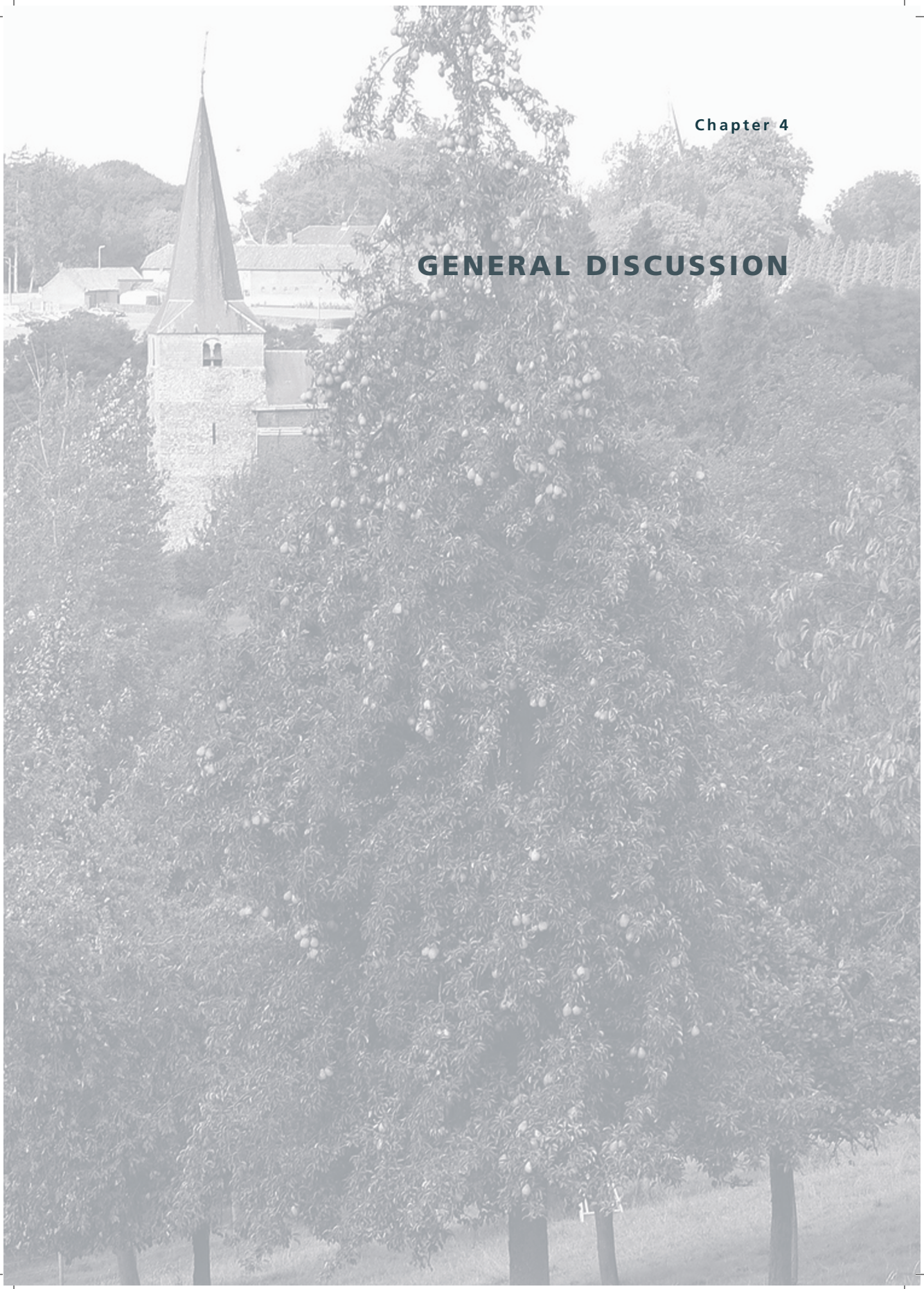
ACH drug load and delirium. The ACH scores of the drugs used by the patients in this study showed a large variability for each of the 6 instruments. There was no association between a patient's total ACH drug load and delirium. The clinical significance of these findings is that there is no single instrument that can be used as an independent guide for quantifying ACH drug load in order to predict delirium caused by the use of different drugs. Investigators should be alert in making a choice for an instrument to assess ACH drug load.

References

1. Inouye SK. Delirium in older persons. N Engl J Med 2006;354:1157-1165
2. Cole MG. Delirium in Elderly Patients. Am J Geriatr Psychiatry 2004;12:7-21
3. Dasgupta M, Dumbrell AC. Preoperative risk Assessment for delirium after noncardiac surgery: a sytematic review. JAGS 2006;54:1578-89
4. Kagansky N, Rimon E, Naor S *et al.* Low Incidence of Delirium in Very Old Patients After Surgery for Hip Fractures. Am J Geratr Psychiatry 2004;12:306-14
5. Ely EW, Gautam S, Margolin R *et al.* The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27:1892-1900
6. McNicoll L, Pisani MA, Zhang Y *et al.* Delirium in the intensive care unit: occurrence and clinical course in older patients. JAGS 2003;51(5):591-598
7. O'Keeffe S, Lavan J. The prognostic significance of delirium in older patients. JAGS 1997;45:174-8
8. Levkoff SE, Evans DA, Liptzin B *et al.* Delirium: the occurrence and persistence of among hospitalised elderly patients. Arch Intern Med 1992;152:334-40
9. Kat MG, Vreeswijk R, de Jonghe JFM *et al.* Long-term cognitive outcome of delirium in elderly hip surgery patients, Dement Geriatr Cogn Disord 2008;26:1-8
10. Inouye SK, Bogardus ST Jr, Charpentier PA *et al.* A multicomponent intervention to prevent delirium in hospitalised older patients. N Engl J Med 1999;340:669-76
11. Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001;62[suppl21]:11-14
12. Lechevallier-Michel N, Molimard M, Dartigues JF *et al.* Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. Br. J Clin Pharmacol 2004;59;2:143-151
13. Moore AR, O'Keeffe ST. Drug-induces cognitive impairment in the elderly. Drugs Aging 1999;15:15-28
14. Han l, McCusker J, Cole M *et al.* Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001;161:1099-1105
15. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. J R Soc Med 2000;93:457-62
16. Tune L, Carr S, Hoag E *et al.* Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry 1992;149(10):1393-4

17. Flacker JM, Cummings V, Mach JR *et al*. The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry 1998;6: 31-41
18. Han L, Agostini JV, Allore HG. Cumulative Anticholinergic Exposure Is Associated with Poor Memory and Executive Function in Older Men. J Am Geriatr Soc 2008;56:2203-10
19. Kalisvaart KJ, de Jonghe JF, Bogaards MJ *et al*. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 2005;53(10):1658-66
20. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalised elderly persons. JAMA 1996;275:852-7
21. Knaus WA, Draper EA, Wagner DP *et al*. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29
22. Folstein MF, Folstein SE, Mc Hugh PR, Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98
23. Tune LE, Holland A, Folstein MF *et al*. Association of postoperative delirium with raised serum levels of anticholinergic drugs. The Lancet 1981; 651-3
24. Carnahan RM, Lund BC, Perry PJ *et al*. The anticholinergic drug scale as a measure of drug-related anticholinergic burden:associations with serum anticholinergic activity. J. Clin Pharmacol. 2006;46:1481-6
25. Carnahan RM, Lund BC, Perry PJ *et al*. The relationship of an anticholinergic rating scale with serum anticholinergic activity in elderly nursing home residents. Psychopharmacology Bulletin: 2002;36(4)14-19
26. Summers WK. A clinical method of estimating risk of drug induced delirium Life Sciences 1978;22:1511-6
27. American Psychiatric Association DSM-IV-TR. Washington DC: American Psychiatric Association; 2000
28. Laurila JV, Pitkala KH, Strandberg TE *et al*. Confusion assessment method in the diagnostics of delirium among aged hospital patients: would it serve better in screening than as a diagnostic instrument. Int J Geriatric Psychiatry 2002;17:1112-9
29. Inouye SK, van Dyck CH, Alessi CA *et al*. Clarifying Confusion: The Confusion Assessment Method. Ann Intern Med 1990;113:941-8
30. Cox EA, Kwatra SG, Shetty S *et al*. Flaws in the serum anticholinergic assay: implications for the study of delirium. JAGS 2009;57:1707-8

31. Campbell N, Boustani M, Limbil T *et al.* The cognitive impact of anticholinergics: A clinical review. Clinical Interventions in Aging 2009;4:225-33
32. Trzepacz PT. The neuropathogenesis of delirium. Psychosomatics 1994;35:374-91
33. Hshieh TT, Fong TG, Marcantonio ER *et al.* Cholinergic Deficiency Hypothesis in Delirium: A Synthesis of Current Evidence. J of Gerontology: Medical Sciences 2008;63A(7):764-72



Chapter 4

GENERAL DISCUSSION

Introduction

Pharmacotherapy is one the most commonly used medical interventions and its progress has contributed significantly to the increase in life expectancy and quality of life during the last century. Many recent studies have revealed the impact of medication errors and the importance of continuity of care in medication management. A significant proportion of drug related problems occurs when patients transition from one healthcare setting to another. Pharmacotherapy across healthcare settings is complicated with multiple physicians prescribing medication at different time-points and patients are often exposed to both intended and unintended medication changes.

The aim of this thesis was to determine the magnitude of medication discontinuities associated with the transitioning of patients between the community setting and the hospital setting and its determinants. Changes to drug regimens are often made during hospitalisation. Of all hospitalised patients taking medication on the day of their admission, 63.1% experienced one or more medication therapy changes during transition, compared to 33.5% of the non-hospitalised reference group (*Chapter 2.1*). The most frequently seen change was a stop (55.2%). Changes in drug treatment also occurred at the time of discharge from the hospital (*Chapter 2.2*). Many patients experienced a discontinuity between the drugs used in the hospital immediately before discharge and the drugs dispensed by an outpatient pharmacy directly following discharge. Of all prescriptions dispensed by the outpatient pharmacy, 40% were not the same as the most recent hospital medication; the most frequent type of discontinuities were product substitution (27%) and start of a new drug (11%). Hospitalisation contributes to an increased likelihood of the initiation of benzodiazepine prescription (*Chapter 2.4*). This risk is highest just before hospitalisation and in the 3 months immediately after hospitalisation. However, hospitalisation was not a determinant of long-term benzodiazepine use. In *Chapter 2.3* we tested the hypothesis that medication unrelated to the reason for hospital admission may often be discontinued during hospitalisation. We calculated the incidence of medication therapy discontinuities for psychotropic drugs used by patients admitted to a hospital for non-psychiatric reasons. Patients using antipsychotic medications showed a 6-fold increase in the incidence of the stopping medication. Within the same therapeutic class, 23.5% of the psychotropic drug treatments that were stopped during hospitalisation were re-prescribed within a time window of 4-12 months after hospitalisation.

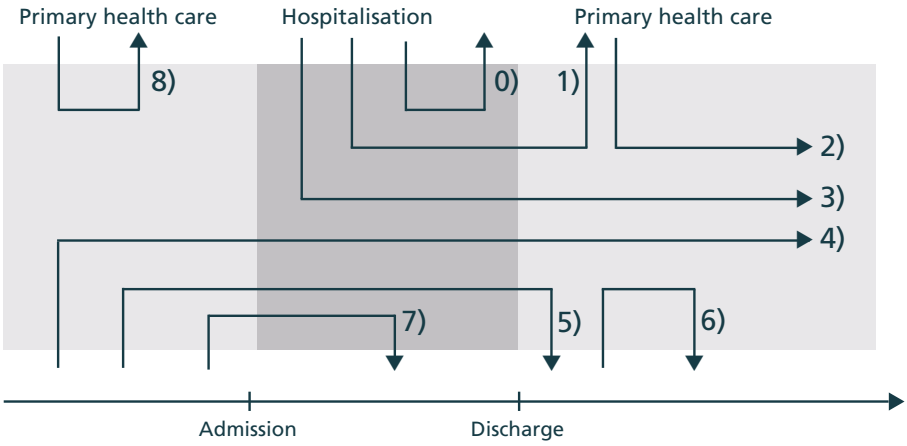


Figure 1. Patterns Of Drug Use Across Health-Care Settings

Prescriptions are defined as medication only available by prescription as opposed to over-the-counter products. Drug use can be subdivided into the following categories:

0) Drugs prescribed during hospitalisation and stopped during hospitalisation

1) Drugs prescribed during hospitalisation and used at discharge but stopped (shortly) after discharge

2) Drugs prescribed after discharge

3) Drugs prescribed during hospitalisation and continued used after discharge

4) Drugs prescribed before hospitalisation and continued use after discharge

5) Drugs prescribed before hospitalisation and discontinued after discharge

6) Drugs prescribed after discharge and discontinued shortly thereafter

7) Drugs prescribed before hospitalisation and discontinued during hospitalisation

8) Drugs prescribed before hospitalisation and discontinued before hospitalisation.

Knowledge of the risk factors for hospitalisation may help to avoid potentially preventable drug-related complications such as hospital admissions. The Chronic Disease Score is an instrument that is associated with the probability of hospitalisation. Because this instrument is based on one-year pharmacy dispensing data, we decided that the number of prescription changes during a 3-month period could also be used as an independent risk factor for hospital admission (*Chapter 3.1*). This Prescription Change Intensity can be added to the established HARM risk factors for hospital admission. In *Chapter 3.2* the various instruments for the assessment of the anticholinergic (ACH) drug load in a group of elderly orthopaedic surgery patients were compared, and there was no association between a patient's total ACH drug load and the risk of delirium.

In this final chapter the studies presented will be examined in a broader context, focusing on two themes i.e. 1) measurement of discontinuities in medication therapy and 2) risk factors that contribute to discontinuities. Finally, some clinical and research implications of the findings will be discussed.

Measurement of medication discontinuity

A main part of pharmacoepidemiological research concerns the study of the etiologic or prognostic relation between drug exposure (determinant) and clinical outcome. A key aspect in such studies is the valid and precise measurement of drug exposure in order to prevent biased findings. In the various chapters presented in this thesis changes in drug use (i.e. (dis)continuities) were the determinant of interest. (Dis)continuities in drug use can be measured using either data from self-reported drug use of the individual patient and/or from administrative databases.[1] Currently, most large-scale studies rely on information about drug exposure extracted from databases originating from systematically collected administrative healthcare data such as general practitioner prescription data (e.g. GPRD, IPCI), pharmacy dispensing data (e.g. PHARMO) or healthcare insurer data. The validity of drug exposure measurement based on pharmacy records has been investigated by Lau *et al.*[2]They concluded that computerised pharmacy records are a reliable reflection of the true drug exposure for drugs that patients used on a chronic basis. Garðarsdóttir described the differences between two types of administrative databases, a prescribing database and a dispensing database.[1] Dispensing databases comprise information on nearly all of the medicines dispensed for each patient regardless of the type of prescribing physician, but these databases often lack information on the reason for the drug prescription and other relevant data such as lifestyle factors. Prescribing databases may also include information on indications, symptoms, co-morbidity, and baseline risk factors. The data from the studies presented in this thesis came from the PHARMO Record Linkage System. (RLS), which was linked to hospital discharge records and can be categorised as a dispensing database.

Administrative data on drug dispensing moments usually do not represent the real life pattern of patient drug taking. The medication history available in a community pharmacy may be incomplete (e.g.due to visits to other pharmacies or the use of over-the-counter products), incorrect (eg, due to post-admission changes not communicated to the community pharmacy),

not reflective of dose changes made between two consecutive prescriptions. or non-adherence.[3,4] Administrative databases often display an irregular drug "pick up" pattern, which can lead to findings of a time gap between two consecutive prescriptions. In most cases, the acceptance level for this time gap is defined and as long as a subsequent prescription falls within a given amount of days after the estimated duration of a prescription, it is considered to belong to the same episode. Gaps seen in dispensing patterns might not necessarily indicate that the drug was not used on gap days. Discrepancies in the true drug exposure may have clinically significant consequences, especially in the elderly population.[5] Most pharmacoepidemiological studies use data on drug exposure from primary care, and many of these datasources are validated as pointed above. In Dutch hospital pharmacies computerised pharmacy records are used as well and these are considered a reliable reflection of a patient's true drug exposure during a hospital stay. These records are different from the databases used in primary care and can be categorised as prescribing databases. Since the prescriptions in these databases are actually orders for a nurse to administer a given medication on a certain moment to a hospitalised patient, this information on drug exposure is considered valid and precise. Formal validation studies are lacking though and could be performed by linking such prescribing data to drug administration data either by direct observed or by electronically registered medication administration. Such validation studies are necessary since studies from the field of medication/patient safety show that often there are unintended discrepancies between the medication prescribed/ordered by the physician and the medication administered by the nurse.

Validation studies of drug exposure data at healthcare transition moments such as the hospitalisations investigated in this thesis are lacking. In the community as well as in the hospital setting there is evidence that prescribing and dispensing information does not completely reflect drug taking, implying imprecision in drug exposure measurement and that this imprecision is larger for (recent) changes (discontinuities) in drug exposure than for continued drug use. Instructions to stop a medication are for example usually not registered in a community pharmacy database. The question is whether this misclassification has influenced our findings. It most likely will have underestimated the absolute prevalence and incidence estimates of discontinuities. Whether this misclassification is differential (i.e. was larger or smaller in the hospitalised group than in the non-hospitalised group) is unknown. However, it is most likely that

imprecision in measuring drug exposure is larger surrounding a hospitalisation, probably towards underestimating the amount of discontinuities. This would mean that the relative risks for discontinuities due to hospitalisation presented in this thesis are underestimated.

The validity of the findings, based on administrative databases are strongly dependent on treatment guidelines and healthcare re-imbursement systems. Substantial changes in either of the two, are likely to change dispensing and prescribing patterns, which can influence the findings. Patients often receive care from different providers, at various locations, and across many levels on the continuum of care. The hospital databases are not integrated with the outpatient databases, therefore, there will be a "black box" period in the longitudinal information about the medication history of a patient. Gaps in the continuity of care constitute an important part of drug related problems.[6] Recently the Dutch National Government has unfortunately decided that a national electronic patient record, including a national pharmacy record will not be implemented, thereby not only hampering continuity of patient care but also pharmacoepidemiological research.

In this thesis we quantitatively studied changes in drug use. In several chapters it was addressed that the reason for such changes was largely unknown i.e. that it was unknown whether changes in medication were the intention of the prescriber or whether it was unintended. Van der Linden *et al* found in a study of 400 hospitalised patients that in 40% of the discontinued medications the reason of discontinuation was not documented.[7] The reasons for changes in medication should be documented in the patient's medication record. Poor documentation and communication of reasons for discontinuing medication may result in the represcription of withdrawn medications. A structured format could be developed in which stops, switches and dosage changes are documented including the (clinical) reason and linking the resulting new prescription to the old prescription as a sequence of events. For example: the currently existing prescription of enalapril 10 mg twice daily was changed by [prescriber] on [date] because of an adverse reaction (cough) to losartan 50 mg twice daily.

Factors associated with discontinuity of drug use and transitioning

An important proportion of drug-related problems occur when patients transition from one health-care setting to another. Nearly every patient is confronted with some form of medication change. There are several factors influencing continuity and discontinuity of drug use at the interface between primary and hospital care. During the mostly short time of hospitalisation the patient will be confronted with at least two transitions and at least 3 moments of (re)prescription and re-evaluation of drug therapy. First, upon admission the preadmission medication regimen should be known and evaluated. During this reconciliation process, intended but also unintended changes in prescribing and transcribing can occur.[5,8] Second, during hospitalisation a natural part of patient treatment is the evaluation of former drug treatment in the context of the patient's (changing) clinical picture and the prescription of new drugs. At discharge, the preadmission medication list will be compared with the current hospital medications in order to create a coherent set of discharge prescriptions *(Chapter 2.2)*. 6 key factors associated with discontinuity of drug use related to patients transitioning to and from the hospital, are discussed.

Figure 2.

Patient

Continuity is essential to intended long-term pharmacotherapy. The decision to start and to continue the use of a drug is made by a physician but the actual execution of a drug regimen is a decision by the patient and is continuously influenced by the way in which patients evaluate their health status and personal need for medication. Many factors can influence the decision making

of patients on whether and how they use their medicines and whether they comply with therapy. These factors differ between patients but also within a single patient over the course of time.[9] Interruptions in dosing can diminish drug action, but the consequences vary by the length of the interruption, the drug formulation, the length of patients' prior exposure to the drug, and the disease being treated.[10] Only 5% of patients maintain continuous daily dosing throughout the year.[11]

From the perspective of the patient, the causes of interruptions or discontinuities in the context of transitioning between healthcare settings can be categorised as follows:

- Changes in drug presentations (e.g. substituting brands for a generic): From a pharmacotherapeutic point of view, these changes are of little relevance but they may be very confusing to the patient when there is poor communication from the physician and pharmacist about these changes in drug presentations.
- Pharmacotherapeutic changes. These changes in drug therapy are all intended changes. Patients can be confused about why a drug has been prescribed, changed in dose or even stopped when no explanation is communicated to the patient about the reasons for these changes.
- Unintended interruptions. These changes can be caused by miscommunication, which will contribute to confusion in patients.

Given the high intensity of intended changes in the short period of hospitalization, it is essential to involve patients in decision making thereof and ensure understanding in order to limit the occurrence of unintended changes in pharmacotherapy.

Physician

Hospital admission or discharge can be complex and challenging for both physicians and patients. Given that hospitalisation is often the result of a worsening of the patient's condition, rational decisions by the physician to optimise the clinical condition of the patient should be the reason for changing medications and therefore, such changes are considered intended. Other intended reasons for discontinuing a drug include the prescribed agent being unnecessary or ineffective, contributing to toxicity or adverse drug reactions, or not being listed in the local (hospital) formulary.[12] Physicians will typically comply with the hospital formulary, which will not always agree with the local formulary. Medication stops can also be intended when drugs are prescribed

for a limited time rather than for chronic use as with antibiotics and analgesics. Studies focusing on medication changes and source discrepancies in relation to either admission to or discharge from the hospital have demonstrated that at those moments new drugs are frequently added to the medication regimens of patients, and medications are often discontinued or substituted [6,13,14] *(Chapter 2.1)*. Unintended discontinuities in the use of medication can result from either a lack of information about the reasons for prescribing the drug or a miscommunication about continuing a prescribed drug therapy.[15-17] Prescribing errors are classified into 3 subcategories: administrative and procedural errors, dosing errors, and therapeutic errors.[18] In particularly in hospitals the administrative procedures may cause non-intended discontinuities because of the complicated process in hospitals from prescribing until administering the drug to the patient. Communication and documentation in hospitals about the reasons of changes in care have to be improved. Van der Linden found in a study of 400 hospitalised patients that in 40% of the discontinued medications the reasons of changing drug use was not documented.[7] Omissions due to hospital physicians forgetting to re-prescribe drugs used by patients at home that were temporarily discontinued during a hospital admission may be caused by lack of reconciliation data at admission and will lead to an unintended drug discontinuity.

In conclusion, the hospital physician is a key factor for intended changes of drug therapy. Without adequate documentation thereof, transfer of the actual medication dossier to the next healthcare provider is hampered increasing the risk of unintended medication changes.

Pharmacist

In the community and out-patient pharmacies the availability of reliable data about prescription drugs is based on data about dispensed medication. This implies that medication not to be dispensed anymore (i.e. stopped medication) or dose changes that can be executed with the medication earlier dispensed usually is not documented as such or only later on in community pharmacies. In the hospital pharmacies the data about drug use is based on data about prescriptions and dose changes and stops are immediately registered. The databases of community or outpatient pharmacies and hospital pharmacies will not always be in conformity which may lead to communication failures between patients, physicians and pharmacists at moments of transition across healthcare settings.

Studies have discussed that improving communication to the community pharmacy improves patient profiles and patient care after hospital discharge.[19,20] However, these studies do not focus on whether medication changes are made clear in community pharmacy records and whether all relevant information, is actually documented. In the study of Van der Linden *et al.* it did not matter whether an adverse drug reaction was mentioned in the discharge letter or not for prevention of re-prescription of inappropriate drugs.[7] This implies that GPs probably did not notice the information on the adverse reaction.[21] The Dutch National Government decided not to introduce a national electronic patient record, including a national pharmacy record. Despite this decision, there is a strong need of development of a universal document for exchange of (pharmacy) data of patients transition across healthcare settings.

Pharmacotherapeutic policy

Differences in pharmacotherapeutic policy between the primary care and the hospital setting may also contribute to discontinuities in medication use among patients. In primary care settings, drug prescriptions are often different from hospital drug formularies within a certain region. These prescriptions differ not only with respect to the choice of the active substance but also with respect to the type of brand for the same active substance. Generally speaking, in the Netherlands, original brands are more frequently used inside the hospital because of both the price discounts on these products and because of the availability of a larger spectrum of product forms. In contrast, outside the hospital, generic prescribing and dispensing is encouraged by government policy and increasingly by insurance companies ('preferentiebeleid'). Drug companies sell their drugs to the hospital at discount prices to ensure the drug will be placed in the hospital's drug formulary. From a pharmacotherapeutic perspective, these changes are of little relevance but they may be as confusing to the patient as a change in active substances.

For many years the use of a local hospital-drug formulary system has been the mainstay of the pharmacotherapy strategy in hospitals. The impact of hospital prescribing on prescribing in general practice is substantial.[22] But the formulary system is being challenged; there has been a gradual decline in the use of the hospital-formulary system.[23] This decline is likely a result of an acknowledgment that it is unnecessary to change therapies for patients receiving long-term drug therapy during a short hospital stay simply to adhere

to the hospital's formulary. Another trend is the increase in the use of clinical practice guidelines that provide not only evidence-based specifications for the selection of specific drugs but also other care variables that are important for the patient including indications, doses, and monitoring criteria. It could be argued that clinical practice guidelines are a more comprehensive way to improve prescribing than the formulary system and represent a logical evolution in quality-improvement strategies. Re-substitution to pre-admission drug use can be a part of the reconciliation process. After discharge, the general practitioner must decide whether or not to maintain the changes in drug therapy that were initiated during a patient's hospital stay. This process can confuse the patient, and there may be a risk of unintended doubling with the medication started during hospital admission and preadmission drug therapy.

Fragmentation of pharmaceutical care

Medical tourism is the practice of patients seeking healthcare services elsewhere.[24] Medical tourism has grown rapidly for the following reasons: (1) inadequate access to local healthcare services, (2) significant regional variability in the cost of healthcare services, (3) the treatment is not covered by local healthcare services, and (4) long waiting period to access services locally. In addition, the widespread use of the Internet has facilitated the growth in medical tourism. Because there are no national electronic patient records in The Netherlands, a consequence of medical tourism is that not all patient medical and pharmaceutical data are registered in the same local databases. In the Netherlands pharmacy shopping is limited. Although Dutch patients are free to get their drugs dispensed at a pharmacy of choice, in general they are loyal to one pharmacy. This loyalty may be because in the Dutch healthcare system, patients were historically closely linked to one pharmacy.[25,26] There are no financial incentives that would motivate a patient to use different pharmacies. However, patients are often made aware of out-patient pharmacies during hospital admission or visit, which gives patients the opportunity to receive their prescribed medication from a second pharmacy with the potential risk of scattering information about the actual medication of the patient between the community pharmacy and the out-patient pharmacy. Self medication (non-prescription drugs) may be considered part of the larger self-care movement whereby individuals undertake activities with the intention of improving health, preventing disease, limiting illness and restoring health after injury or illness. Self medication has largely been associated with the use of non-prescription drugs (sometimes referred to

as over-the-counter medications) which can be purchased in pharmacies and in retail outlets. These drugs can be used without the advice of a physician or pharmacist. Gaps in communication about non-prescription drugs or lack of any information about the use of these drugs can result in adverse drug reactions or drug interactions.[27]

Communication

Medication-related problems occur at the interfaces of care settings. To evaluate clinical drug effects physicians and pharmacists must have a comprehensive picture of current medication use of patients. During a hospitalisation the home medication regimen of patients is often continued. Ideally, the process of obtaining a medication history involves the integration of information from several sources, including the patient him/herself. Dispensing databases usually do not always represent the actual pattern of patient medication use when changes that occur in the time between two consecutive prescriptions are not registered in the database of a patient's community pharmacy. In addition, inaccurate or incomplete medication histories obtained at hospital admission may lead to medication errors such as unexpected interactions or failure to detect drug-related problems.[28] Incomplete medication information at the time of hospital discharge may also generate unintended medication discrepancies between the medications used before admission and those used after discharge.[29]

Patients are often discharged from the hospital on drug therapy regimes that differ from those used before hospitalisation.[30-32] (*Chapter 2.1*) At discharge the current medication regimens needs to be reconciled; newly started medication that was only required during the hospitalisation (eg. for preventing of venous thrombo-embolism or stress ulcers) should be stopped.[33] During the period of transition between healthcare settings, adequate transfer of information about the reasons for the discontinuation of drug therapy is required. Karapinar *et al* confirmed the needs of general practitioners regarding discharge medication. Dutch general practitioners want to be informed on discharge medication on the day of discharge with information on reasons for changes and discontinuations.[34] Loss of information due to poor communication between hospitals and primary care physicians can result in the re-prescription of medication that was stopped intentionally during the hospital admission (*Chapter 2.3)* or continuing medication that should have been stopped. Omissions due to hospital physicians

forgetting to prescribe drugs used at home that were temporarily discontinued during hospital admission are frequently seen and may be caused by lack on reconciliation data at hospitalisation.

Implications for clinical practice and future research clinical practice

- Every medication change should be documented in a structured format including in information about the reasons for changing and indications for newly started medications both in hospital and general practice.
- Dispensing of non-prescription drugs that carry a risk for side effects or drug interactions should only be done by pharmacies that can add the dispensed drug to the patients' medication history.
- Because the patient is currently the only constant factor in the healthcare system, the patient should play a central role in communication and information about his drug use by taking care of his medication file.
- Development of a uniform single national patient medication record that is accessible to all healthcare providers.
- Development of a clinical rule by selecting those patients who are at risk for changes in disease severity and hospitalisation. For this goal the Prescription Change Intensity can be used. The total ACH drug load can not be used to predict delirium caused by the use of different drugs.
- Abolishing of the 'Preferentiebeleid' (preference-policy) of the insurance companies and introducing another system to regulate costs of pharmaceutical care.
- Integrating the hospital drug formulary with the local (regional) drug formulary in primary care.
- Empowering of the introduction in hospitals of the process of reconciliation of actual drug use at admission and discharge from the hospitals and facilitating financial incentives for it.

Future research

- In *Chapter 2.3* of this thesis we found that medication unrelated to the reason for hospital admission may often discontinued during hospitalisation. The reasons of these discontinuations should be further studied.
- Patients transitioning between healthcare settings introduces unintended discontinuities in drug use, whether these discontinuations lead to a worsening health and a longer hospital stay should be investigated.
- Discontinuities in drug use associated with hospitalisation occur both in primary care as well as in hospital setting. Studies should be performed if there is a difference in risk profiles between those two settings.
- Development of a universal definition for discontinuities.
- Additional research is needed to unravel the factors contributing to unintended discontinuities.
- Validation of the reconciliation process of actual drug use as well at discharge as several weeks after discharge.

Conclusion

Transition into or out of the hospital is a vulnerable period with respect to changes in drug use. Patients transferred from the primary care setting to the hospital setting (or the reverse) may experience considerable (unintended) modifications to their drug regimen during and pre-and post-hospitalisation. Regardless of the patient's movement through different healthcare settings, the prescribed medications should be consistent with his or her therapeutic needs. Notwithstanding the questions that remain, we hope that this thesis will give more attention on medication discontinuities in patients transitioning between healthcare settings.

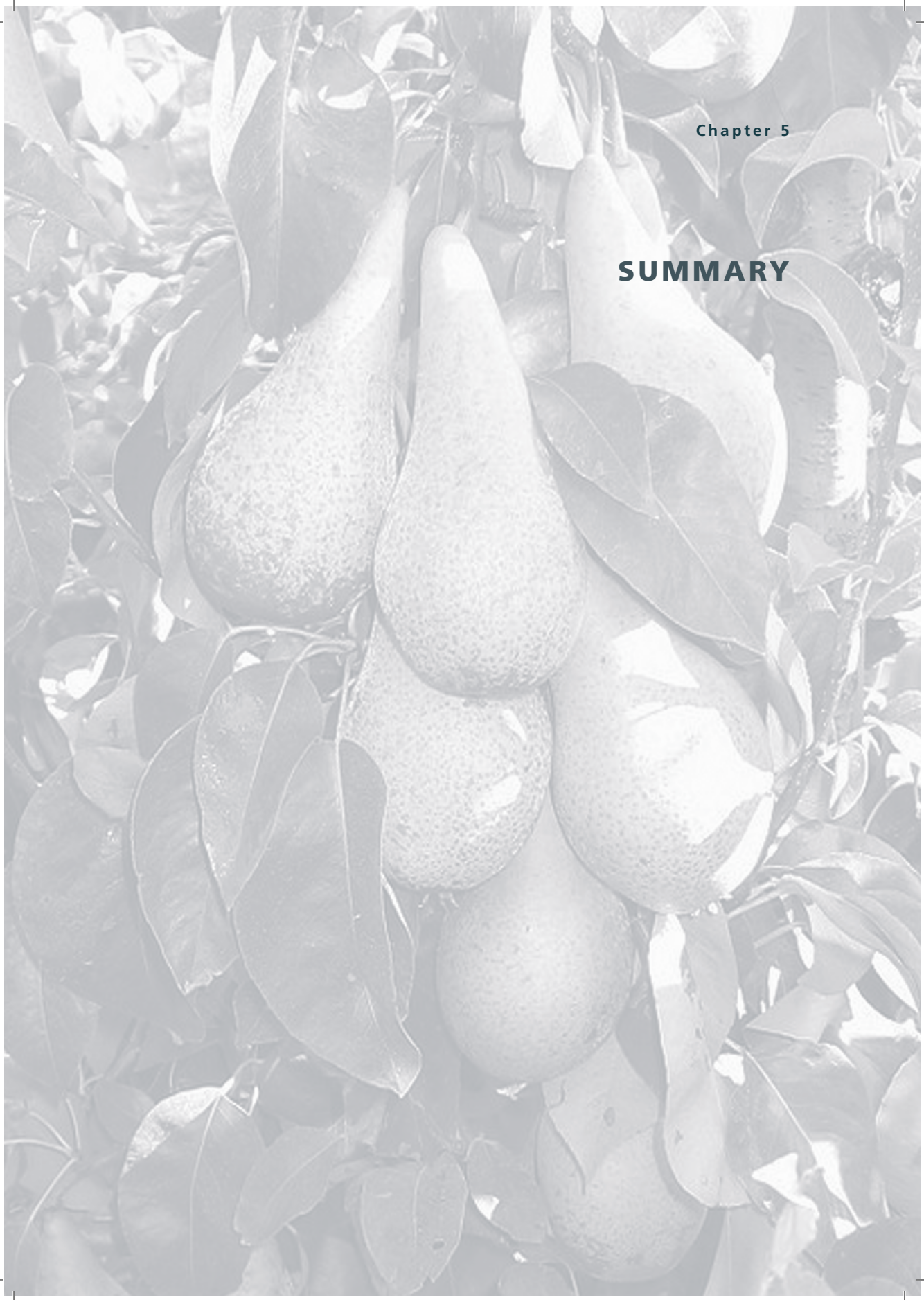
References

1. Garðarsdóttir H. Drug treatment episodes in pharmacoepidemiology - antidepressant use as a model.[Dissertation] Utrecht: University of Utrecht 2009
2. Lau HS, De Boer A, Beuning KS, Posrius A.Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50;5:619-25
3. Buurma H, Bouvy ML, De Smet PA, Floor-Schreudering A, Leufkens HG, Egberts ACG. Prevalence and determinants of Pharmacy shopping behaviour. J Clin Pharm Ther 2008;33:17-23
4. Lowe CJ, Petty DR, Zermansky AG, Raynor DK. Development of a method for clinical medication review by a pharmacist in general practice. Pharm World Sci 2000;22:121-6
5. Steurbaut S, Leemans L, Leysen T, De Baere E, Cornu P, Mets T, Dupont AG. Medication history reconciliation by clinical pharmacists inn elderly inpatients admitted from home or a nursing home. Ann Pharmacother 2010;44:1596-1603
6. Cochrane RA, Mandal AR, Ledger-Scott M, Walker R. Changes in drug treatment after discharge from hospital in geriatric patients. Br Med J 1992;305;253-7
7. Van der Linden CM, Jansen PA, Van Geerenstein EV, Van Marum RJ, Grouls RJ, Egberts ACG, Korsten EH. Reasons for discontinuation of medication during hospitalization and documentation thereof: a descriptive study of 400 geriatric and internal medicine patients. Arch Intern Med 2010;10(12):1085-7
8. Karapinar-Carkit F, Borgsteede SD, Zoer J, Smit HJ, Egberts ACG, Van den Bemt MLA. Effect of medication reconciliation with and without patient counselling on the number of pharmaceutical interventions among patients discharged from the hospital. Ann Pharmacother 2009;43:1001-10
9. Van Geffen K. Initiation, execution and discontinuation of antidepressant therapy, considerations and decisions of patients. [Dissertation] Utrecht: University of Utrecht 2008
10. Osterberg LG, Urquhart J, Blaschke TF. Understanding forgiveness: minding and mining the gaps between pharmakokinetics and therapeutics Clinical Pharmacology & Therapeutics 2010;88(4):457-9
11. Vrijens B, Vincze G, Kristanto P, Urqhart J, BurnierM. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically completed dosing histories. BMJ 2008;336:1114-7
12. Himmel W, Talabache M, Kochen MM. What happens to long-term medication when general practice patients are referred to hospital. Eur J Clinical Pharmacol 1996;50:235-7
13. Grimes TC, Duggan CA, Delaney TP, Graham IM, Conlon KC, Deasy E, Jago-Byrne MC, O'Brien P. Medication details documented on hospital discharge:

cross-sectional observational study of factors associated with medication non-reconciliation. Br J Clin Pharmacol 2011;71(3):449-57

14. Himmel W, Kochen MM, Sorns U, Hummers-Pradier. Drug changes on the interface between primary and secondary care. Int J Clin Pharmacol and Therap 2004;42(2):103-9
15. Glintborg B, Hillestrom PR, Olsen LH, Dalhoff KP, Poulsen HE. Are patients reliable when self-reporting medication use. Validation of structured drug interviews and home visits by drug analysis and prescription data in acutely hospitalised patients. J Clin Pharmacol 2007;47(11):1440-9
16. Kripalani S, Jackson AT, Schnipper JL, Coleman EA. Promoting effective transitions of care at hospital discharge: a review of key issues for hospitalists. J Hosp Med 2007;2(5):314-23
17. Kripalani S, LeFevre F, Philips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians- Implications for patient safety and continuity of care. JAMA 2007;297(8):831-41
18. Fijn R, Van den Bemt PMLA, Chow MC, De Blaey CJ, De Jong. Van den Berg LTW, Brouwers JRBJ. Hospital prescribing errors: epidemiological assessment of predictors. Br J Clin Pharmacol
19. Gray S, Urwin M, Woolfrey S, Harrington B, Cox J, Copying hospital discharge summaries to practice pharmacists: does this help implement treatment plans. Qual Prim Care 2008;16(5):327-34
20. Kuehl AK, Chrischilles EA, Sorofman BA. System for exchanging information among pharmacists in different practice environments. Am J Health Syst Pharm 1998;55(10):1017-24
21. Van der Linden CM, Kerskes MC, Bijl AM, Maas HA, Egberts ACG, Jansen PA. Represcription after adverse drug reactions in the elderly: a descriptive study. Arch Intern Med 2006;166(150);1666-7
22. Stuffken R, Egberts ACG, van Schaik BAM. Insight in specialistic prescription Registration of outpatient medication and discharge medication. Pharm Weekbl 2001;136(11):390-4
23. Pedersen CA, Schneider PJ, Scheckelhoff DJ ASHP national survey of pharmacy practice in hospital settings: prescribing and transcribing 2007. Am J Health Syst Pharm 2008;65:827-43
24. Khalid AJ, AL Khaja-Reginald P, Sequeira- Awatif H, Damanhori H. Polypharmacy associated with medical tourism: a critique on drug therapy. Int J Clin Pharm 2011;33:61-5

25. Buurma H, Pharmacy shopping: determinants and the relation with heavy use of psychotropic drugs [dissertation] Utrecht: University of Utrecht, 2006
26. Monster TB, Janssen WM, de Jong PE, de Jong-van den Berg LT. Pharmacy data in epidemiological studies: an easy to obtainand reliable tool. Pharmacoepidemiol Drug Saf 2002;11:379-84
27. Hughes CM, McElnay JC, Fleming GF. Benefits and risks of self medication. Drug Saf (2001)24:1027-1037
28. Rozich JD, Resr RK. Medication safety: one organisation's approach to the challenge. J Clin Outcomes Manage 2001;8:27-34
29. Avery A, Witherington EM, Pirzada O. Communication gaps and readmissions to hospital for patients aged 75 Years and older: observational study. Qual Saf Health Care 2008;17(1):71-5
30. Munday A, Kelly B, Forrester JW, Timoney A, McGovern E. Do general practitionersand community pharmacists want information on the reasons for drug therapy changes implemented by secondary care. Br J Gen Pract. 1997;47(422):563-6
31. Bellingham C. How to improve medicines management at the primary secondary interface. Pharm J 2004;272:210-11
32. Van der Kam WJ, Meyboom de Jong B, Tromp TF, Moorman PW, van der Lei J. Effects of electronic communication between the GP and the pharmacist. The quality of medication data on admission and after discharge. Fam Pract 2001;18(6):605-9
33. Holzmueller CG, Hobson D, Berenholtz SM, et al. Medication reconciliation: are we meeting the requirements. JCOM 2006;13:441-4
34. Karapinar F,Van den Bemt PMLA, Zoer J, Nijpels G, Borgsteede SD. Informational needs of general practitioners regarding discharge medication: content, timing and pharmacotherapeutic advices. Pharm World Sci 2010;32:172-7



Chapter 5

SUMMARY

Pharmacotherapy is one the most commonly used medical interventions, and advances in pharmacotherapy have significantly contributed to the increases in life expectancy and quality of life that occurred during the last century. Many recent studies have revealed the impact of medication errors and the importance of continuity of care in medication management. A significant proportion of drug-related problems occur when patients transition from one healthcare setting to another. With transition across health care settings, nearly every patient is confronted with some form of medication discontinuity. Care transitions are a natural occurrence in our healthcare system. During a single episode of an illness, patients may visit multiple care settings and be treated by different healthcare professionals. Transitions from one healthcare setting to another are associated with intentional and unintentional changes in patient care. During the short time of hospitalisation, the patient will be confronted with at least two transitions and at least three moments of (re)prescription and re-evaluation of drug therapy. First, upon admission, the preadmission medication regimen should be documented and evaluated. Second, during hospitalisation, a natural part of a patient treatment is the evaluation of any former drug treatment in the context of the patient's (changing) clinical status and the prescription of new drugs. Finally, at discharge, the preadmission medication list will be compared with the current hospital medications to create a coherent set of discharge prescriptions.

The aim of this thesis was to determine the magnitude of medication discontinuities associated with the transitioning of patients between the community setting and the hospital setting and to identify the determinants of these discontinuities.

We assessed the association between hospitalisation and medication therapy discontinuities *(Chapter 2.1)*. We conducted a retrospective follow-up study in a study population of 8,681 hospitalised patients and an equal number of matched non-hospitalised patients. Among all hospitalised patients taking medication on the day of their admission (n=5,265), 63.1% of patients had one or more medication therapy discontinuities at the date of admission compared to 33.5% of the non-hospitalised patients. The most frequent change in the hospitalised group was a cessation of medication therapy (55.2%). The highest relative risk was found for a therapeutic switch [RR 5.34 (95% CI 3.93-7.26)] followed by product substitution [RR 2.32 (95% CI 1.88-2.86)] and stop [RR 1.98 (95% CI 1.85-2.13)]. Changes in drug treatment occurred at the time of discharge from the hospital *(Chapter 2.2)*. Many patients experienced a discontinuity between the drugs that were used in the hospital immediately before discharge

and the drugs that were dispensed by an outpatient pharmacy directly following discharge. Among all prescriptions that were dispensed by an outpatient pharmacy, 40% were not the same as the most recent hospital medication. The most frequent type of discontinuities were product substitution (27%) and new prescriptions, starting at the moment of discharge (11%). Product substitution was primarily caused by the substitution of the brand-name drugs used during hospitalisation with generic drugs.

In *Chapter 2.3*, we tested the hypothesis that a medication that was unrelated to the reason for hospital admission often shows discontinuities during hospitalisation. We calculated the incidence of medication therapy discontinuities for psychotropic drugs that were used by patients who were admitted to a hospital for non-psychiatric reasons. For this study, we used the same database as described in *Chapter 2.1.* The subjects were patients using psychotropic drugs at hospitalisation and at 6 control time points. Psychotropic drugs were defined as drugs of the ATC groups N05A (antipsychotics) and N06A (antidepressants). On the index date, we found no significant differences in the incidence of medication discontinuities for the hospitalised and non-hospitalised patients due to product substitution [adj. RR 0.68 (95% CI 2.28-17.7)] or therapeutic switch [adj. RR 0.99 (95% CI 0.35-2.79)]. The incidence of medication stop was significantly increased [adj. RR 2,42 (95% CI 1.65-3,54)]. Subgroup analyses of medication discontinuities on the date of admission revealed that patients using antipsychotic medications had a six-fold higher incidence of any discontinuity of medication [adj. RR 6.28 (95% CI 2.28-17.7)]. In conclusion, patients using antipsychotic medication who are admitted to the hospital for a non-psychiatric disease are at high risk for discontinuity of these drugs. A represcription rate in the subgroup of patients in whom psychotropic use was stopped during admission was calculated. Within the same therapeutic class, 23.5% of the psychotropic drugs that were stopped during hospitalisation were re-prescribed within a time window of 4-12 months after hospitalisation.

Several studies have suggested that hospitalisation may be a determinant for the initial and subsequent long-term use of benzodiazepines. However, previous studies have indicated conflicting evidence. We conducted a study to determine whether hospitalisation induces initiation of benzodiazepine use and subsequent long-term use *(Chapter 2.4).* In this study, we examined benzodiazepine prescriptions, which were defined as prescriptions for a benzodiazepine (ATC N05BA and N05CD) or benzodiazepine-related hypnotic or sedative (N05CF) drug. Long-term use was defined as a period of consecutive use that spanned

more than 180 days as determined from the date of initial prescription. One of the most interesting findings of this study is the strong association between hospitalisation and the initial prescription of benzodiazepines in the time window of three months just before and after admission, with an Incidence Density Ratio (IDR) of 4.81 (95% CI 4.08-5.67). However, the relative risk for long-term use (more than 180 days) over the entire study period was slightly higher, although not significant, [RR 1.04 (95% CI 0.95-1.13)] among hospitalised patients than among non-hospitalised patients. Within 3 months before and after hospitalisation, the relative risk for long-term use was lower for the hospitalised patient group [RR 0.82 (95% CI 0.69-0.98)].

Knowledge of the risk factors for hospitalisation may help prevent drug-related complications such as hospital admissions. The Chronic Disease Score is an instrument that is associated with the probability of hospitalisation. Because this instrument is based on one-year pharmacy dispensing data, we tested the hypothesis that the number of prescription changes during a 3-month period could be used as an independent risk factor for hospital admission. We assessed the Prescription Change Intensity (PCI) for the hospitalised and non-hospitalised groups *(Chapter 3.1)*. In this study, we confirmed the association between the PCI and hospital admission [OR 4.1 (95% CI 3.1-5.1) for the PCI category ≥4 prescription changes at 3 months before hospital admission]. The PCI score could function in the ambulatory setting as an indicator of increased hospitalisation risk and could be used in medication safety programs.

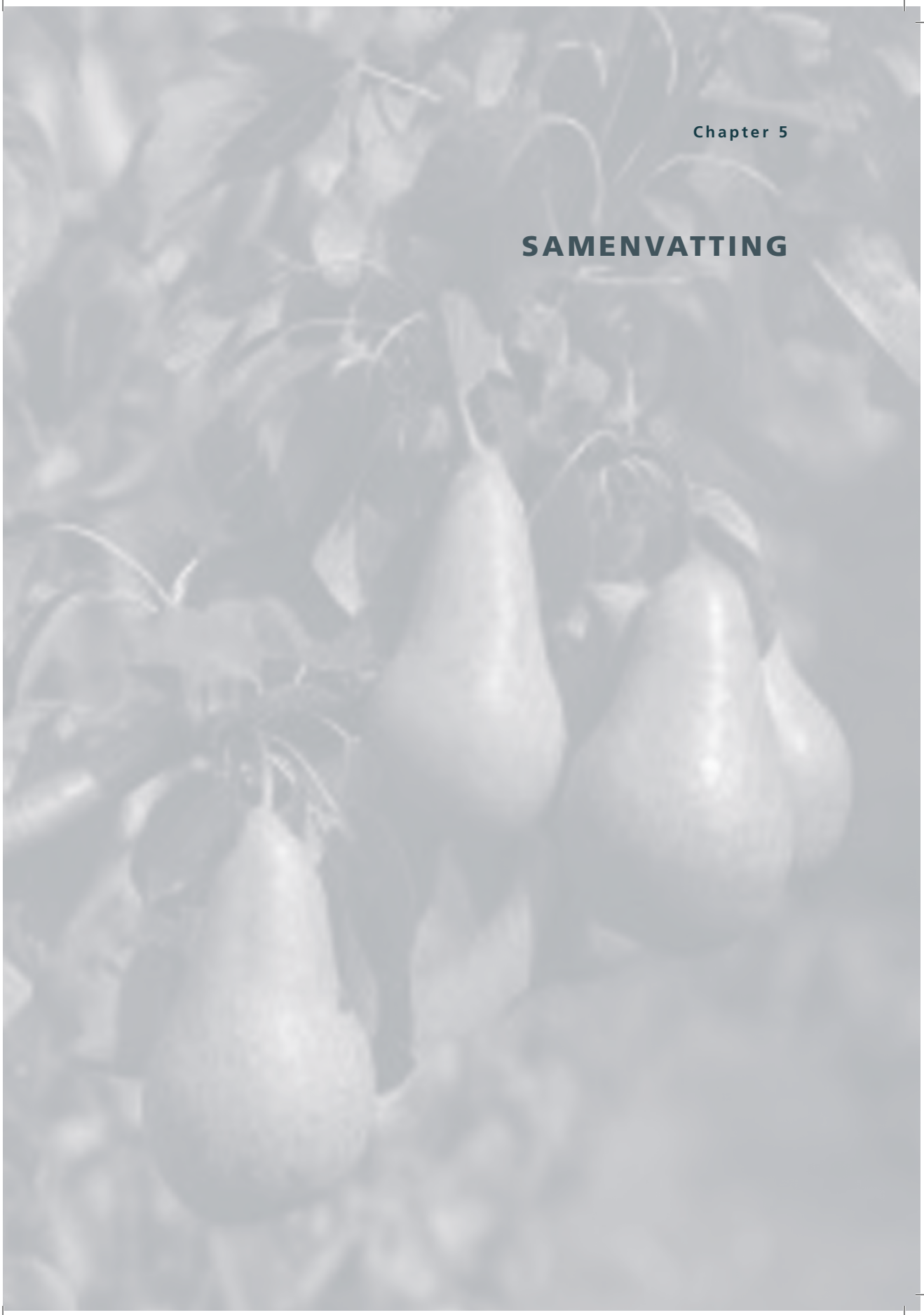
In *Chapter 3.2,* the different instruments for the assessment of anticholinergic (ACH) drug load were compared to assess the association of the aggregate ACH drug load with the occurrence of delirium in a cohort of elderly orthopaedic surgery patients. The ACH load was quantified by assigning an ACH score to the selected drugs. We selected 6 different instruments to assign the ACH score: two instruments that were based on a receptor binding study, one instrument that was based on drug characteristics and clinical experience, one instrument that was based on the use of the Scientific Institute of Dutch Pharmacies database, one instrument that was based on the EMEA Summary of Product Characteristics and one instrument that was based on a consensus rating of an expert panel. The ACH scores of the selected drugs in this study showed a large variability for each of the 6 instruments. We detected large discrepancies between the 6 instruments in classifying drugs into "none", "low", "intermediate", or "high". We found no association between a patient's total ACH drug load and delirium. The clinical significance of these findings demonstrated that no single

instrument can be used as an independent guide for quantifying the ACH drug load and predicting delirium caused by the use of different (ACH) drugs.

In the general discussion of *Chapter 4,* two topics are discussed in a broader context:

1. Factors that estimate the measurement of medication discontinuities, and
2. Factors that were associated with the discontinuity of drug use and transitioning. We provided recommendations for clinical practice and for future research.

In conclusion, transitions in care are vulnerable periods for patients with respect to discontinuities in drug use. Regardless of the patient's movement through different healthcare settings, the prescribed medications should be consistent with his or her therapeutic needs. We hope that this thesis will provide more insight regarding drug use and transitions between health care settings.



Chapter 5

SAMENVATTING

Met het publiceren in 1999 van het rapport "To err is human, building a safer Health System" door het Institute of Medicine te Washington, is veel belangstelling ontstaan voor patiëntveiligheid. Het rapport gaat in op medische fouten in het algemeen; echter een belangrijk deel van deze medische fouten wordt veroorzaakt door het onjuist gebruik van geneesmiddelen. Recente studies verwoorden het belang van continuïteit in de zorgverlening. Transitie van patiënten tussen zorgverleners of transitie van patiënten tussen de diverse echelons in de gezondheidszorg komt frequent voor in de huidige structuur van onze gezondheidszorg en geeft vaak aanleiding tot fouten en verwarring bij de patiënt en zorgverlener. Gedurende een soms korte periode van onderzoek en/of behandeling kan de patiënt geconfronteerd worden met verschillende zorgverleners uit soms ook nog verschillende instituten. Bij ziekenhuisopname krijgt de patiënt te maken met ten minste twee transitie momenten, nl van de 1e lijn naar de 2e lijn en weer terug van de 2e lijn naar de 1e lijn; daarnaast kan er sprake zijn van overplaatsing naar een andere afdeling binnen het ziekenhuis, De door de patiënt gebruikte medicatie wordt bij deze transities op een drietal momenten geëvalueerd. Bij opname wordt het op dat moment actuele gebruik vastgelegd. Daarna worden tijdens de opname de noodzakelijke aanpassingen aangebracht in de gewenste medicatie op basis van klinische bevindingen. Tenslotte wordt bij ontslag beoordeeld welke medicatie die in de kliniek voorgeschreven was, gecontinueerd moet worden, ook rekening houdend met de gebruikte medicatie vóór ziekenhuisopname. Deze transities in de zorg kunnen de oorzaak zijn van discontinuïteiten in voorgeschreven medicatie. Deze discontinuïteiten kunnen gewenst, maar ook onbedoeld zijn als gevolg van b.v. slechte communicatie tussen zorgverleners bij overdracht van patiënt gegevens.
De doelstelling van het onderzoek beschreven in dit proefschrift is om de relatie tussen ziekenhuisopname en het gebruik van (voorgeschreven) geneesmiddelen in kaart te brengen. Daarnaast wordt in breder verband stilgestaan bij factoren, die van invloed zijn op het vaststellen van medicatie-discontinuïteiten. Tot slot wordt besproken, welke factoren van invloed zijn op de relatie tussen transities en discontinuïteiten.

Hoofdstuk 1 is een algemene inleiding waar wordt ingegaan op het voorschrijven van geneesmiddelen en de continuïteit van zorg.

In *Hoofdstuk 2.1* wordt de associatie beschreven tussen ziekenhuisopname en discontinuïteit van in de 1e lijn gebruikte medicatie. We hebben een retrospectief vervolg onderzoek uitgevoerd binnen de PHARMO database met patiëntgegevens over de periode juni 1998 tot en met juni 2000. Cases waren patiënten opgenomen in het ziekenhuis (=index datum). Bij iedere case werd een controle patiënt gezocht zonder ziekenhuisopname maar die met de cases overeen kwamen wat betreft geboortejaar, geslacht en geografische regio. In het onderzoek werden uiteindelijk 8.681 patiënten en een gelijk aantal controle patiënten geïncludeerd. Er werden vier discontinuïteiten gedefinieerd: generiek/ specialité substitutie, product substitutie (zelfde werkzame stof, maar andere sterkte of farmaceutische toedieningsvorm), therapeutische switch (dezelfde eerste vier karakters van de betreffende Anatomical Therapeutic Chemical [ATC] code) en het stoppen van de medicatie.Van de patiënten, die op de dag van ziekenhuisopname geneesmiddelen gebruikten (n=5.265) vertoonde 63.1% een discontinuïteit in medicatie in vergelijking met 33.5% van de niet opgenomen patiënten (relatieve risico [RR] 1.82; 95% betrouwbaarheidsinterval 1.71-1.94) De meest voorkomende discontinuïteit was het stoppen van medicatie (55.2%), het hoogste relatieve risico werd vastgesteld voor de therapeutische switch (RR 5.34; 95% betrouwbaarheidsinterval 3.93-7.26) We concludeerden, dat ziekenhuisopname geassocieerd is met een verhoogde kans op discontinuïteit van in de eerste lijn gebruikte medicatie.

In *Hoofdstuk 2.2* wordt beschreven welke veranderingen bij ontslag uit het ziekenhuis nog plaatsvinden bij de in de in kliniek voorgeschreven medicatie.Voor dit onderzoek werden vergeleken de medicatie, die de patiënt in het ziekenhuis gebruikte op de dag van ontslag en de medicatie die als "ontslagrecept" door een polikliniek apotheek werd afgeleverd.Van alle door de polikliniek apotheek afgeleverde medicatie kwam 40% niet overeen met de medicatie van de patiënt op de dag van ontslag. De meest gesignaleerde discontinuïteit was product substitutie (27%, zelfde werkzame stof, maar andere sterkte of farmaceutische toedieningsvorm of generiek substitutie). Nieuwe medicatie, gestart op het moment van ontslag, maakte 11% uit van het aantal afgeleverde medicaties. Het voor product substitutie gevonden percentage wordt in dit onderzoek vooral veroorzaakt door generieke substitutie.

In *Hoofdstuk 2.3* wordt de hypothese getest dat medicatie die niet is gerelateerd aan de reden van ziekenhuisopname, een verhoogde kans loopt op een discontinuïteit bij opname van de patiënt in het ziekenhuis. Om de hypothese te testen analyseerden we het voorkomen van medicatie discontinuïteiten van psychofarmaca bij patiënten, die voor een niet psychiatrische indicatie werden opgenomen in het ziekenhuis. Voor dit onderzoek gebruikten we dezelfde PHARMO database als beschreven in *Hoofdstuk 2.1.* Cases waren patiënten, die bij opname in het ziekenhuis (index datum) en op zes andere tijdsmomenten psychofarmaca (antipsychotica of antidepressiva) gebruikten. De controlegroep bestond uit patiënten, die deze psychofarmaca gebruikten en niet in het ziekenhuis opgenomen werden. Uitgesloten werden patiënten die opgenomen werden met een psychiatrische indicatie. Alleen voor de discontinuïteit "stop" werd een significant verhoogde incidentie waargenomen op de index datum (gecorrigeerd [adj] RR 2.42; 95% betrouwbaarheidsinterval 1.65-3.54). Subgroep analyse van de discontinuïteit "stop" naar therapeutische groep verklaarde, dat de discontinuïteit stop met name gerelateerd was aan het gebruik van antipsychotica (adj RR 6.28; 95% betrouwbaarheidsinterval 2.28-17.7). Van alle op de index datum gestopte psychofarmaca werd 23.5% binnen 4-12 maanden weer herstart met hetzelfde middel of een middel uit dezelfde therapeutische groep.

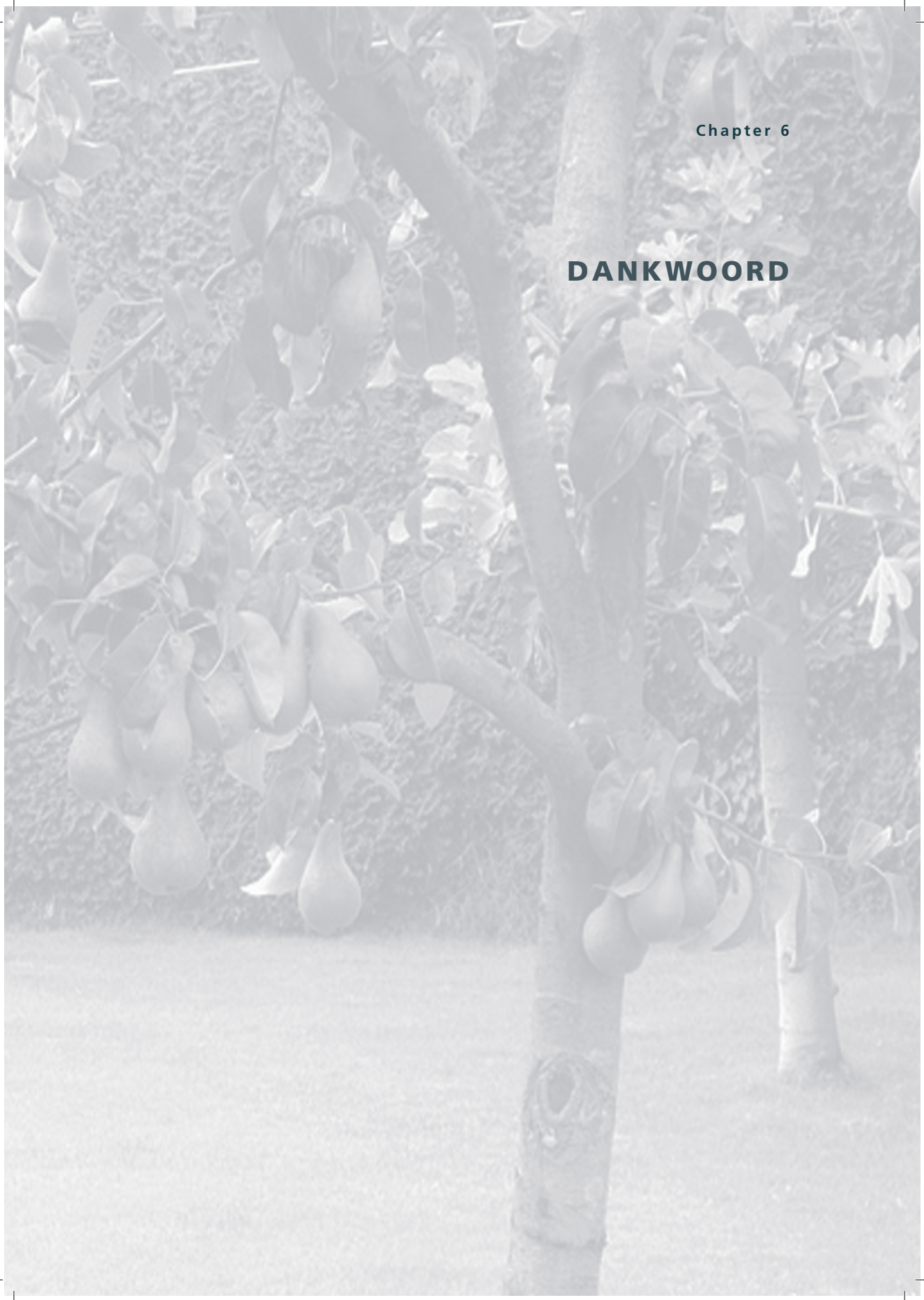
In *Hoofdstuk 2.4* wordt het voorschrijven van benzodiazepinen (BZDs) in relatie tot ziekenhuisopnames bestudeerd. Onderzocht werd of ziekenhuisopname aanleiding geeft tot een verhoogd aantal eerste voorschriften van BZDs. Daarnaast werd onderzocht of deze eerste voorschriften aanleiding gaven tot een langdurig gebruik. Gebruik werd gemaakt van de in hoofdstuk 2.1 beschreven PHARMO database. BZDs werden gedefinieerd als middelen uit de ATC groep N05BA, N05CD en BZDs gerelateerde hypnotica en sedativa (ATC N05CF). Als analyse periode werd genomen een periode van 18 maanden voor en 18 maanden na de index datum. Een nieuw BZD voorschrift werd gedefinieerd als een voorschrift voor een BZD waarbij in een periode van 6 maanden voor betreffend voorschrift geen BZD werd gebruikt. De incidentie van eerste voorschrift voor een BZD werd berekend voor de in het ziekenhuis opgenomen patiëntengroep en voor de niet opgenomen groep en uitgedrukt als het aantal eerste BZD voorschriften per 100 patiëntenjaren. Over de gehele studieperiode van 36 maanden bedroeg het relatieve risico voor een nieuw BZD voorschrift, uitgedrukt als Incidence Density Ratio [IDR] 1.97 (95%

betrouwbaarheidsinterval 1.84-2.10). Het relatieve risico drie maanden voor en drie maanden na de index datum bedroeg 4.81 (95% betrouwbaarheidsinterval 4.08-5.67). Langdurig gebruik van BZDs, gedefinieerd als gebruik langer dan 180 dagen was in de in het ziekenhuis opgenomen patiëntengroep over de gehele studieperiode niet significant frequenter dan in de niet opgenomen groep. In de periode van drie maanden voor en drie maanden na de index datum is het relatieve risico voor langdurig gebruik in de groep van opgenomen patiënten significant lager dan in de niet opgenomen groep van patiënten. (0.82, 95% betrouwbaarheidsinterval 0.69-0.98). Uit dit onderzoek mag geconcludeerd worden dat een verhoogd risico bestaat op het starten van BZD medicatie in de periode van drie maanden voor en drie maanden na ziekenhuisopname, maar dat dit geen aanleiding geeft tot een langdurig gebruik van deze middelen.

In *Hoofdstuk 3.2* is onderzocht of het aantal medicatie wijzigingen per periode van drie maanden (Prescription Changes Intensity [PCI]) gebruikt kan worden als een onafhankelijke risico factor voor ziekenhuisopname.Voor dit onderzoek werden dezelfde PHARMO gegevens en opzet gebruikt, zoals beschreven in *Hoofdstuk 2.1*. Gedefinieerd werden vier classificaties van discontinuïteiten; verandering van dosering van hetzelfde middel, switch, stoppen of starten met een nieuw middel. De PCI werd omschreven als het aantal discontinuïteiten in medicatie over een periode van drie maanden. Gemeten werd het aantal wijzigingen op de meetmomenten 3,6,9,12 en 18 maanden voor de index datum. Voor het aantal medicatie veranderingen per tijdseenheid werd de PCI ingedeeld in vier verschillende categorieën van aantal discontinuïteiten. Geconcludeerd werd dat het risico van ziekenhuisopname toeneemt met het aantal medicatiewijzigingen per tijdseenheid. (PCI categorie 1 wijziging, Odds ratio [OR] 1.4; 95% betrouwbaarheidsinterval 1.3-1.5 en PCI categorie ≥4 wijzigingen, OR 4.1 betrouwbaarheidsinterval 3.1-5.1). Omdat de Chronic Disease Score [CDS] ook een relatie heeft met ziekenhuisopname, is de CDS vergeleken met de PCI. De CDS is gebaseerd op de aflevergegevens van chronische medicatie over een periode van 1 jaar. De gevonden correlatie tussen PCI en CDS is gering. Deze studie geeft aan dat de PCI gebruikt kan worden als een risico factor voor ziekenhuisopname naast de reeds bestaande HARM – risicofactoren.

In *Hoofdstuk 3.2* is het gebruik van anticholinerge [ACH] geneesmiddelen en het optreden van een delier bij patiënten, die een electieve orthopedische operatie ondergaan, bestudeerd.. Gebruik werd gemaakt van studiegegevens van een studie naar het effect van haloperidol- profylaxe op het voorkomen en op de ernst en duur van een delier bij electieve orthopedische patiënten. Vergeleken werden een zestal verschillende meetmethoden om de ACH lading van de gebruikte geneesmiddelen vast te stellen. De totale ACH belasting van de gebruikte medicatie werd per patiënt berekend m.b.v. de zes meetmethoden. De onderzoeksgroep bestond uit 397 patiënten. Door deze patiënten werden in totaal 185 verschillende geneesmiddelen gebruikt. Bij 68 patiënten ontwikkelde zich een delier. Het optreden van een delier en de totale ACH lading van de gebruikte geneesmiddelen vertoonde geen correlatie. Bij de vergelijking van de verschillende meetmethoden werd vastgesteld, dat er grote verschillen tussen de verschillende meetmethoden bestaat in toekenning van ACH lading aan geneesmiddelen. De klinische significantie van dit onderzoek is dat geen enkele meetmethode als onafhankelijke risicofactor aangehouden kan worden om een delier te voorspellen bij orthopedische patiënten die een electieve operatie ondergaan.

Hoofdstuk 4 omvat een algemene discussie waarbij de resultaten van de individuele onderzoeken in dit proefschrift in een breder perspectief worden geplaatst. Een tweetal onderwerpen worden bediscussieerd: 1) factoren, die het meten van medicatie discontinuïteiten beïnvloeden; 2) factoren, die van invloed zijn op de associatie tussen transities in de zorg en discontinuïteiten. Tot slot worden de klinische implicaties en mogelijkheden voor toekomstig onderzoek besproken.
Als conclusie mag worden getrokken, dat continuïteit van zorg een belangrijk kwaliteits- en veiligheidsaspect is van onze gezondheidszorg. Transities in de gezondheidszorg geven aanleiding tot geplande en niet geplande discontinuïteiten.
We hopen, dat dit proefschrift meer inzicht geeft in de oorzaken van deze discontinuïteiten.



Chapter 6

DANKWOORD

Met de presentatie van dit proefschrift wordt een bijzondere periode afgesloten. Ik heb het voorrecht gehad, wetenschappelijk onderzoek te mogen combineren met de dagelijkse praktijk van de ziekenhuisfarmacie. Dat creëerde kansen, maar had ook zijn beperkingen.
Wat is er mooier om bevindingen uit onderzoek direct te kunnen spiegelen aan de dagelijkse praktijk in de eigen kliniek. Het steeds maar moeten omschakelen van enerzijds bezig zijn met onderzoek en anderzijds verantwoordelijk zijn voor dagelijkse beslommeringen van een ziekenhuisapotheek viel bij tijd en wijlen niet mee. Steeds heb ik voor ogen gehouden, dat mij wel unieke kansen werden geboden. Deze kansen hadden niet aangegrepen kunnen worden zonder de hulp van een aantal mensen die –elk op hun eigen wijze- hebben bijgedragen aan dit proefschrift. In het bijzonder wil ik de volgende mensen bedanken

Allereerst wil ik mijn promotor en co-promotor bedanken voor hun inzet en steun, die ik steeds van hen mocht ontvangen.
Prof. Dr. A.C.G. Egberts, beste Toine. Het begon allemaal met een gesprek tussen de roulette tafels in Las Vegas. Jij was geïnteresseerd in data uit de periferie en ik liep met de wens, meer tijd te kunnen besteden aan wetenschappelijk onderzoek. Met het realiseren in Hilversum van een polikliniek apotheek beseften we beiden, dat we direct toegang kregen tot gegevens over de transmurale farmacie en dat daar dus kansen lagen. Je hebt mij geleerd, hoe je een onderzoeksvraag moet oppakken en uitwerken. Ook als ik in een dip zat wist je mij altijd op een positieve manier te stimuleren. Manuscripten waar van alles aan mankeerde, wist je te retourneren met positieve en stimulerende kanttekeningen. Ik ben er trots op, dat je mijn promotor hebt willen zijn.

Dr. E.R. Heerdink, beste Rob. Soms gingen zaken wel erg snel; maar dan stond jij er om op een gelegen moment nog eens rustig uitleg te geven. Jij hebt het vermogen een lastige vraag te vertalen naar een praktische en oplosbare vraag. Aan gezelligheid ontbrak het je niet; bij meerdere ISPE congressen mochten we samen optrekken en ondervond ik veel steun van je bij voordrachten. Te samen met Toine waren jullie voor mij een gouden duo. Zonder dat had het resultaat er heel anders uitgezien.

Dr. P.C. Souverein, beste Patric. Bij diverse hoofdstukken van dit proefschrift ben je betrokken geweest. Je was altijd laagdrempelig toegankelijk voor vragen

bij het ontrafelen van grote databestanden. Ook voor ondeskundige vragen had je altijd oor en hielp je me op het goede pad. Bedankt voor je waardevolle ondersteuning.

Alle andere promovendi en medewerkers van de afdeling Farmaco-epidemiologie en Klinische Farmacologie wil ik bedanken voor de gezelligheid en goede sfeer op de afdeling. In het bijzonder gaat dank uit naar Willem Rekveld, die altijd klaar stond om problemen met computerprogramma's op te lossen. Speciale dank gaat ook uit naar het secretariaat. Beste Anja, Ineke en Suzanne (en voorheen Addy), dank voor de hulp en het steeds weer opnieuw regelen van een werkplek voor mij als "gastmedewerker".

Grote erkentelijkheid ben ik verschuldigd aan de Raad van Bestuur van Tergooiziekenhuizen In het bijzonder de voorgangers van de huidige Raad van Bestuur, Chiel Huffmeijer en Jens Goossen. Jullie creëerden voor mij de mogelijkheid het werk als ziekenhuisapotheker te combineren met een onderzoeksopdracht aan de universiteit. Ik heb dat altijd als een groot voorrecht beschouwd.

Ik wil de ziekenhuisapothekers van Tergooiziekenhuizen, Petra Bestebreurtje, Gijsje Boeke Madelon Butterhoff, Willemien Lagas, Paul van der Linden en Jolande van der Wildt, danken voor hun interesse en hulp. Ik heb vanaf het begin gekozen om mijn promotieonderzoek zoveel mogelijk in het "Utrechtse" uit te voeren. Het gevolg was dat ik regelmatig afwezig was; jullie wisten mijn afwezigheid echter op adequate wijze op te vangen. Naast de huidige collega's wil ik ook Frouke Mulder en Jan van Oostveen bedanken voor de periode,waarin ze deel hebben uitgemaakt van het team ziekenhuisapothekers van Tergooiziekenhuizen. Dank ook aan de collega in opleiding en projectapothekers: Kris van Keulen, Bart Hendriks en Verena Mulder en verschillende andere projectapothekers uit voorgaande jaren.

Het begon allemaal met de opstart van een polikliniek apotheek in destijds Ziekenhuis Hilversum. Graag wil ik het veelvuldig overleg in de opstartfase met Bart Postema als directeur van de polikliniek apotheek memoreren. Bart, we hebben samen aan de farmacie in het Gooi een nieuwe dimensie toegevoegd: de transmurale farmacie. Laten we de uitdagingen daarbij met beide handen aangrijpen.

Drs. CGM. Sino, beste Carolien, samen mochten we onderzoeken of het aantal medicatie veranderingen een risicofactor is voor ziekenhuisopname. Jij hebt mij geleerd ook vanuit het perspectief van een verpleegkundige naar dit onderwerp te kijken. Bedankt voor de constructieve en prettige samenwerking.

Voor het kritisch meelezen en meedenken bij diverse manuscripten de afgelopen jaren waren verschillende personen betrokken. In het bijzonder wil ik bedanken Prof.dr. Marieke Schuurmans, dr. Rolf van Hulten en dr. Fred de Koning en dr. Kris Movig.
Voor het beschikbaar stellen van het databestand om de associatie tussen delier en het gebruik van "anticholinerge" geneesmiddelen vast te stellen ben ik veel dank verschuldigd aan Kees Kalisvaart en Ralf Vreeswijk. In het expert-panel (hoofdstuk 3.2) participeerden Carolien van Rees, Rob van Marum en Marieke Kerskes, waarvoor veel dank

Madelon Butterhoff– Terlingen, beste Madelon, ik wil je bedanken voor het uitvoeren van je registratieonderzoek voor de opleiding tot ziekenhuisapotheker in het kader van mijn promotieonderzoek. Hoofdstuk 3.2 was niet mogelijk geweest zonder jouw bijdrage.

Alle leden van de leescommissie (Prof.dr. M.L. Bouvy, Prof.dr. LT.W. de Jong-van den Berg, Prof.dr. H.G.M. Leufkens, Prof.dr. L. Lie-A-Huen en dr. P.M.L.A.van den Bemt) wil ik hartelijk danken voor de inhoudelijke beoordeling van mijn manuscript.

En tot slot een woordje tot mijn meest dierbare familieleden. Lieve Jaap, Marije en Marguaritha. De thuisbasis ontgroeid en twee boefjes als kleinkinderen. Wat ben ik er trots op dat Jaap en Marguaritha als paranimfen mij terzijde willen staan. We gaan het beleven.
Last but not least mijn lieve Bonna. Jij steunde mij door dik en dun in mijn onderzoek ambitie naast het werk in de ziekenhuisapotheek. Ook in moeilijke periodes bleef je positief en stimulerend. Maar ik besef, dat ik er af en toe meer had moeten zijn. Gaan we nu intenser genieten van dat flesje wijn bij de open haard ????

Chapter 6

LIST OF CO-AUTHORS

Co-authors of manuscripts presented in this thesis

Affiliations during the conductance of the research.

Madelon Butterhoff – Terlingen

* Tergooi Hospitals, Department of Clinical Pharmacy, Blaricum/ Hilversum, The Netherlands.

Toine C.G. Egberts

* Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht, The Netherlands
* University Medical Centre Utrecht, Department of Clinical Pharmacy, Utrecht, The Netherlands

Eibert R Heerdink

* Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht, The Netherlands
* University Medical Centre Utrecht, Department of Clinical Pharmacy, Utrecht, The Netherlands

Rolf P van Hulten

* Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht, The Netherlands
* Apotheek van Hulten, Joure, The Netherlands

Kees J Kalisvaart

Kennemer Gasthuis Haarlem, Department of Geriatric Medicine, Haarlem, The Netherlands

Marieke CH Kerskes

* Catherina Hospital, Department of Clinical Pharmacy, Eindhoven, The Netherlands

Fred HP de Koning

* Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht, The Netherlands

Rob J van Marum

* University Medical Centre Utrecht, Department of Geriatric Medicine, Utrecht, The Netherlands
* Jeroen Bosch Hospital, Department of Geriatric Medicine, 's-Hertogenbosch, The Netherlands

Kris LL Movig

* Medisch Spectrum Twente, Department of Clinical Pharmacy, Enschede, The Netherlands

Carolien van Rees

* Tergooi Hospitals, Department of Geriatric Medicine, Blaricum/ Hilversum, The Netherlands

Marieke J Schuurmans

* University Medical Centre Utrecht, Department of Rehabilitation, Nursing Science and Sports, Utrecht, The Netherlands
* University of Applied Sciences Utrecht, Research Centre for Innovation in Health care. Utrecht, The Netherlands

Carolien GM Sino

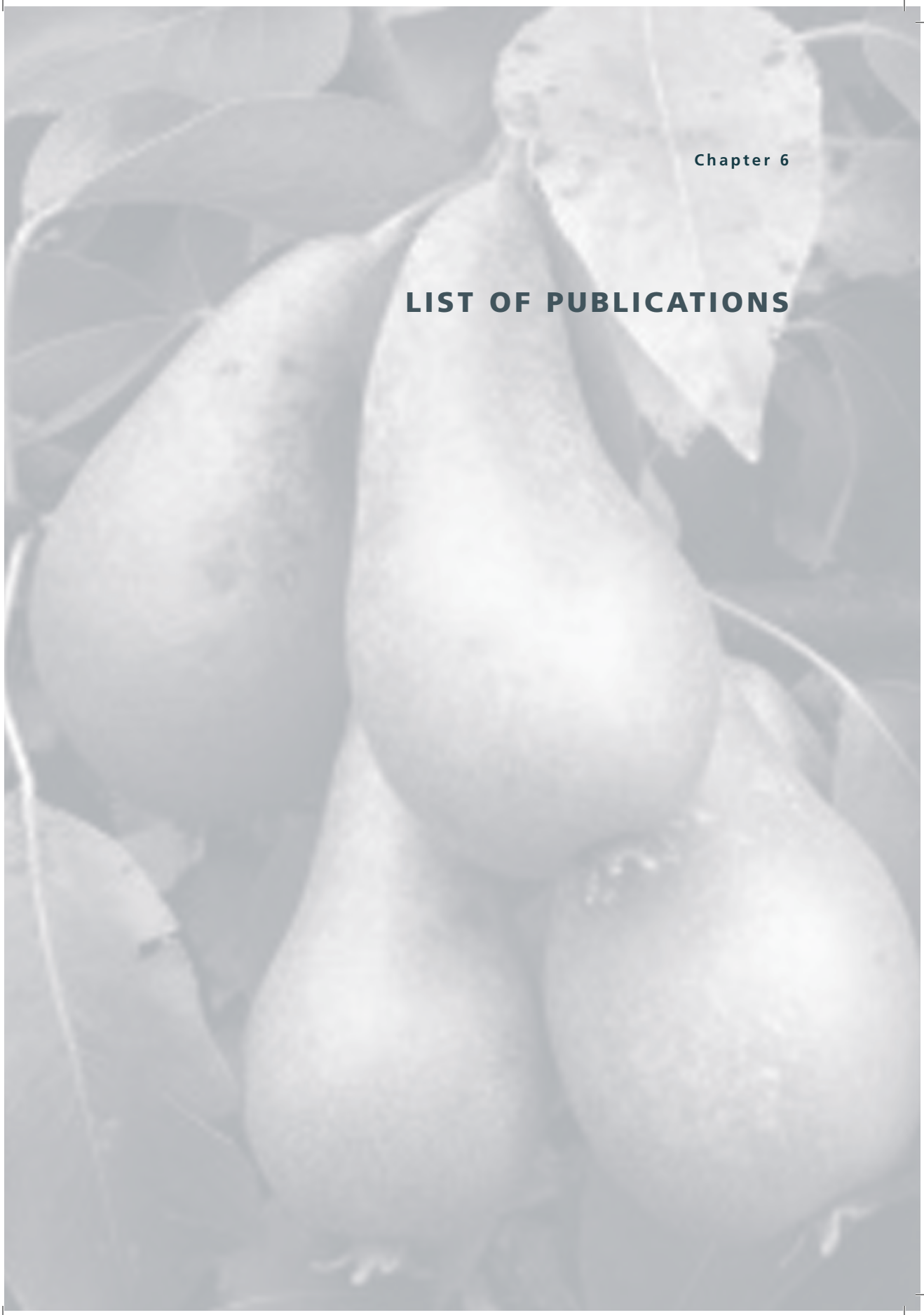
* University of Applied Sciences Utrecht, Research Centre for Innovation in Health care. Utrecht, The Netherlands

Patric C Souverein

* Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht, The Netherlands

Ralph Vreeswijk

* Kennemer Gasthuis Haarlem, Department of Geriatric Medicine, Haarlem, The Netherlands



Chapter 6

LIST OF PUBLICATIONS

Publications related to this thesis

Butterhoff-Terlingen MH, Stuffken R, Egberts ACG, Heerdink ER, van Marum RJ, Kalisvaart KJ.
Measurement of anticholinergic drug burden with various instruments and association with occurence of delirium in elderly orthopaedic surgical patients.
Pharm Weekbl. Wetenschappelijk Platform 2009;3(10):178-82

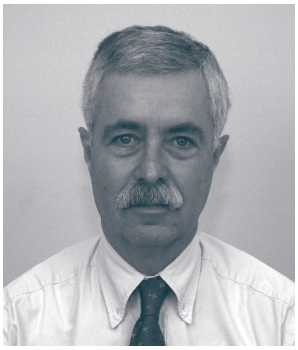
Stuffken R, Heerdink ER, de Koning FHP, Souverein PC, Egberts ACG.
The association between hospitalisation and discontinuity of medication therapy used in the community setting in the Netherlands.
Ann Pharmacother 2008;42:933-9

Stuffken R, van Hulten RP, Heerdink ER, Movig KLL, Egberts ACG.
The impact of hospitalisation on the initiation and long-term use of benzodiazepines.
Eur J Clin Pharmacol 2005;61:291-5

Stuffken R, Egberts ACG.
Discontinuities in drug use upon hospital discharge
Pharm World Sci 2004;26:268-70

Stuffken R, van Schaik BAM, Egberts ACG.
Inzicht in specialistische receptuur.
Pharm Weekbl 2001;136(11):390-4

Curriculum Vitae



Rutger Stuffken was born on 11 August 1947 in Heerlen, The Netherlands.
He completed secondary school (HBS-B) at the "Grotius College" in Heerlen in 1965 and obtained his pharmacy degree in 1974 at the University of Groningen. In 1974, he started as a hospital pharmacist trainee at the Clinical Pharmacy Department of "de Weezenlanden" and "Sophia" Hospitals in Zwolle under the supervision of drs. M.H. Voorhuis and drs. D. Andringa. He had a position as a registered hospital pharmacist in the "Diakonessenhuis Hilversum" since 1978 and in the fusion hospitals "Hilversum Hospital" and "Tergooiziekenhuizen" in later years. During those years, he had different positions as a hospital pharmacist with a focus on manufacturing drugs, as chief pharmacist, and as a hospital pharmacist responsible for logistics and purchasing drugs. Since 2005, he has been responsible for the education of trainee hospital pharmacists at the Tergooi Hospitals.
He combined his work as a hospital pharmacist with PhD research at the Division of Pharmacoepidemiology & Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences of Utrecht University (Prof A.C.G. Egberts, Dr. E.R. Heerdink).
Rutger Stuffken is married to Bonnie Naber. They have one son, Jaap (1979) and one daughter, Marguaritha (1981).

Henley on Thames
1970
Ladies Challenge Plate