



**Detection and prevention of drug related problems
in older hospitalized patients -
the ~~role of~~ challenge for the clinical pharmacist**

**Thesis submitted in fulfillment of the requirements
for the degree of Doctor in Medical Sciences**

ANNEMIE SOMERS

June 2012

Ghent University

Faculty of Medicine and Health Sciences

Promoter: Prof. dr. M. Petrovic

Co-promoter: Prof. H. Robays

PROMOTER

Prof. dr. M. Petrovic
Department of Internal Medicine, Faculty of Medicine and Health Sciences, Ghent University

CO-PROMOTER

Prof. H. Robays
Department of Pharmaceutical Analysis, Faculty of Pharmaceutical Sciences, Ghent University

OTHER MEMBERS OF THE STEERING COMMITTEE

Em. Prof. dr. M. Bogaert
Department of Pharmacology, Faculty of Medicine and Health Sciences, Ghent University

Prof. dr. A. Dupont
Department of Pharmacology, Faculty of Medicine and Pharmacy, Free University of Brussels

MEMBERS OF THE READING COMMITTEE

Prof. dr. L. Van Bortel
Department of Pharmacology, Faculty of Medicine and Health Sciences, Ghent University

Prof. dr. A. Spinewine
Centre for Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Université Catholique de Louvain

Prof. dr. T. Mets
Department of Gerontology, Faculty of Medicine and Pharmacy, Free University of Brussels

Prof. dr. K. Boussery
Department of Pharmaceutical Care, Faculty of Pharmaceutical Sciences, Ghent University

MEMBERS OF THE EXAMINING COMMITTEE

Prof. dr. T. van der Cammen
Department of Internal Medicine, Faculty of Medicine, Erasmus University Rotterdam, the Netherlands

Prof. dr. E. Mortier
Department of Anaesthesia, Faculty of Medicine and Health Sciences, Ghent University

Prof. dr. T. Christiaens
Department of General Practice and Primary Health Care, Faculty of Medicine and Health Sciences, Ghent University

Prof. dr. J. Vande Walle
Department of Paediatrics, Faculty of Medicine and Health Sciences, Ghent University

TABLE OF CONTENT

LIST OF ABBREVIATIONS.....	4
INTRODUCTION.....	5
1. GENERAL INTRODUCTION.....	5
2. INTRODUCTION TO THE RESEARCH AND WHAT IS ALREADY KNOWN	8
3. AIM OF THIS RESEARCH AND OVERVIEW OF THE DIFFERENT CHAPTERS	11
CHAPTER 1: REPORTING ADVERSE DRUG REACTIONS ON A GERIATRIC WARD: A PILOT PROJECT	19
ABSTRACT.....	20
INTRODUCTION.....	21
METHODS.....	21
RESULTS	25
DISCUSSION.....	26
CONCLUSION.....	30
TABLES.....	31
REFERENCES.....	35
APPENDICES	37
CHAPTER 2: CONTRIBUTION OF DRUG RELATED PROBLEMS TO HOSPITAL ADMISSION IN THE ELDERLY..	39
ABSTRACT.....	40
INTRODUCTION.....	41
METHODS.....	41
RESULTS	44
DISCUSSION.....	45
CONCLUSION.....	49
TABLES.....	50
REFERENCES.....	54
APPENDICES	56
CHAPTER 3: THE USE OF HYPNOSEDATIVE DRUGS IN A UNIVERSITY HOSPITAL: HAS ANYTHING CHANGED IN TEN YEARS TIME?.....	57
ABSTRACT.....	58
INTRODUCTION.....	59
METHODS.....	60
RESULTS	62
DISCUSSION.....	65
CONCLUSION.....	69
TABLES.....	70
REFERENCES.....	74

CHAPTER 5-4: EVALUATION OF CLINICAL PHARMACIST ADVICES RECOMMENDATIONS AT THE GERIATRIC WARD IN A BELGIAN UNIVERSITY HOSPITAL	76
ABSTRACT.....	77
INTRODUCTION.....	79
METHODS.....	79
RESULTS	82
DISCUSSION.....	84
CONCLUSION.....	87
TABLES.....	88
REFERENCES.....	92
CHAPTER 4 5: APPLICABILITY OF AN ADAPTED MEDICATION APPROPRIATENESS INDEX (MAI) FOR DETECTION OF DRUG RELATED PROBLEMS IN GERIATRIC INPATIENTS	93
INTRODUCTION.....	95
METHODS.....	96
RESULTS	98
DISCUSSION.....	99
CONCLUSION.....	103
FIGURES AND TABLES.....	105
REFERENCES.....	110
DISCUSSION AND GENERAL CONCLUSION	112
1. MAIN FINDINGS	112
2. LIMITATIONS OF THIS RESEARCH.....	115
3. STRENGTHS OF THIS RESEARCH	117
4. RECOMMENDATIONS FOR THE FUTURE AND FOR FURTHER RESEARCH	118
5. PERSPECTIVES.....	119
6. REFERENCES.....	122
SUMMARY.....	123
LIST OF PUBLICATIONS	124

List of abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ATC	Anatomic Therapeutic Chemical classification
CI	Confidence Interval
CNS	Central Nervous System
CVI	Content Validity Index
CYP450	Cytochrome P450
DRHA	Drug Related Hospital Admission
DRP	Drug Related Problem
DTF	Drug Therapy Failure
HSs	Hypnotosedatives
ICC	Intraclass Correlation Coefficient
LOS	Length of stay
MAI	Medication Appropriateness Index
po%	overall percentage of agreement
p-marg	marginal agreement
p-neg	negative agreement
p-pos	positive agreement
PIM	Potential Inappropriate Medication
SADR	Serious Adverse Drug Reaction
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences

Introduction

1. General introduction

In this dissertation, the issue of drug related problems in older hospitalized patients is addressed. The following definition for drug related problems (DRPs) is often used: 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes' ^[1]. Another approach for DRPs is the division into three categories i.e. 'overuse', 'misuse' or 'underuse' of medicines ^[2]. The scope of drug related problems occurring in older patients however varies between studies ^[3-10]. Adverse drug reactions (ADRs) are most often included; these are defined as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function' (WHO definition) ^[11]. Besides ADRs, also drug therapy failures due to inadequate dose or non-compliance are sometimes considered, as well as inappropriate drug choice, untreated indications and drug use without indication. Drug therapy potentially leading to drug related problems is often called 'inappropriate prescribing' and is particularly hazardous for older patients ^[12-14]. In different studies it has been shown that older patients indeed suffer more often from drug related problems than middle-aged patients ^[3;5;6;9;15].

Various factors can explain the high incidence of drug related problems in older persons ^[15-21]. Firstly, older people often suffer from different diseases, and consequently are treated with many drugs, with a higher risk of adverse reactions and drug-drug interactions. Secondly, changes in pharmacokinetic and pharmacodynamic properties make older persons more prone to the occurrence of drug related problems. Thirdly, older patients are often treated by multiple healthcare professionals, in particular different prescribing physicians. Therefore, it can be difficult to keep an overview of the different medications prescribed in terms of indications, duration of therapy, monitoring of adverse reactions and follow-up of the effectiveness of the drugs for the different medical problems. Fourthly, decreased capability to handle drugs (e.g. taking tablets out of blisters, or inhalation techniques) can lead to decreased compliance and inappropriate drug therapy.

Older persons are usually prescribed the same drugs as younger people, but these drugs can work differently in older people, and are also more frequently combined ^[22-24]. In particular, the following drugs are considered hazardous in older people:

- drugs for the central nervous system (hypnotics, antipsychotics, antidepressants,...), particularly due to possible deterioration of cognitive function;
- drugs with sustained release or with a long half-life, due to reduced renal function (and/or hepatic function);
- drugs with a narrow therapeutic-toxic index, due to impairment of the homeostatic control mechanisms and greater sensitivity to factors such as fever and vomiting;
- combinations of drugs that are metabolized by CYP450, due to increased risk of drug-drug interactions;
- drugs with anticholinergic properties due to impaired cholinergic transmission in the aging brain;
- drugs that can cause orthostatic hypotension, due to the frequent occurrence of orthostasis and consecutive gait and balance disorders and risk of falls.

The clinical impact of drug related problems in older persons is illustrated by the high incidence of drug related hospital admissions. Although older patients are often hospitalized at acute geriatric wards with professional care including evidence based drug therapy, the risk of drug related problems during hospitalization is still present ^[14;15;25;26]. The prolongation of the pharmacotherapy initiated before hospital admission, in combination with the acute treatment during admission makes the drug scheme often complex, not only due to numerous drugs but also with regard to the need for careful evaluation of which medicines should be continued, changed, temporarily or definitely stopped, and which drugs should be started with follow-up of effects and side-effects.

When addressing the issue of drug related problems, an important point is the clarification and positioning towards the concept of 'medication errors'. According to the definition, a medication error concerns preventable incorrect drug use that may lead to clinical harm (and this can happen

during the whole drug process of prescribing, delivering, preparing, administering and follow-up of drug therapy) ^[27]. As for medication errors, the focus lies on the preventable aspect and therefore a preventable drug related problem can be considered as a medication error. There is no doubt that there is no strict separation between the two concepts and in practice it is not clear when a drug related problem becomes a medication error (e.g. a patient with good renal function is prescribed an antibiotic at a usual dose; thereafter the renal function decreases and the dose should be reduced; there is now a drug related problem concerning an inappropriate dose; however, when the dose is not reduced after a certain period of time, this becomes a medication error).

In order to define preventive strategies for drug related problems in older people, we must look at the factors explaining a high frequency of DRPs in older patients. The factor concerning different prescribing physicians underlines the need for careful evaluation of drug therapy within medication review processes. Hospital admission of older patients therefore could be the ideal moment to take a close look at the drug regimen in order to avoid misuse, overuse and underuse. Moreover, moments of transition between care settings (e.g. unplanned hospital admission or discharge from hospital to the community) can lead to unintended discrepancies of the drug list, and to drug related problems after discharge.

Various methods have been described to promote appropriate drug prescribing in older persons ^[28;29]. These aim at avoiding potentially dangerous drugs, assessing the appropriateness of drug therapy in a systematic way, multidisciplinary geriatric evaluation teams, and clinical pharmacist's advices. Another approach which could be helpful for more appropriate prescribing throughout the hospital (also for younger patients) is computerized physician order entry, more specifically with tools for assisted prescribing and with alerts when possible drug related problems are detected. Clinical pharmacy activities have been initiated in Belgium around ten years ago in different university hospitals, but have been enlarged since the Belgian government finances pilot projects with the aim of assessing the impact and demonstrating the added value of clinical pharmacy.

2. Introduction to the research and what is already known

In this thesis five studies will be presented about the incidence and types of drug related problems in older hospitalized patients, and about a patient centred and pharmacist driven method to detect these problems in order to reduce clinical harm.

2.1. Drug related problems in older hospitalized patients

As mentioned in the introduction, older people are more prone to the occurrence of adverse drug reactions. These can lead to hospital admission, or can occur during hospitalization because of worsening condition, multiple diseases or drug-drug interaction. The reported percentages of ADRs in hospitalized patients vary between 2.4% and 10.9% ^[30;31]. However, older patients usually take a higher number of drugs in comparison to younger patients, which is a well-known risk factor for developing adverse drug reactions. At the same time, it is a well-known problem that voluntary ADR reporting systems is characterized with important under-reporting ^[32;33]. Therefore, when studying the incidence of ADRs, efforts should be made to combine spontaneous ADR reporting by different caregivers (physicians and nurses), with information taken directly from the patient, e.g. by interview during the ward visit.

When searching the literature, a wide range of drug related hospital admissions (DRHAs) is reported, with percentages varying between 4 and 30%. The majority of these problems concerns ADRs, with avoidability ranging between 50% to 97% ^[3;9;13]. A prospective multicenter HARM study (Hospital Admissions Related to Medications) was performed in the Netherlands, in which 13000 unplanned hospital admissions were screened and of which 5.6% were medication related ^[34]. The results show that the mean age of the drug related admissions was significantly different (68 years) from the mean age of all unplanned admissions (60 years). Furthermore, a number of risk factors were identified, which all apply to older patients, i.e. impaired cognition, multimorbidity, increased dependency, impaired renal function and non-adherence to the medication regimen.

The following problems seem to contribute often to hospitalization in older patients:

- bleeding due to the use of anticoagulants and non-steroidal anti-inflammatory drugs

- dehydration and electrolyte disturbances due to diuretics
- falls due to the intake of central nervous system drugs (hypnotics, antipsychotics, antidepressants)
- osteoporosis and fractures due to the prolonged use of corticosteroids
- hypoglycaemia due to oral antidiabetic drugs and insulin, and hyperglycaemia related to the intake of corticosteroids
- heart failure and renal failure due to non-steroidal anti-inflammatory drugs
- constipation due to the use of narcotic analgesics
- bradycardia and orthostatic hypotension related to the intake of beta blocking agents.

2.2. Tools for detection of drug related problems in older patients

Since older patients are more vulnerable to adverse drug-related events, there is a need to ensure appropriate prescribing in order to prevent misuse, overuse and underuse of drugs. Different tools and strategies have been developed to reduce inappropriate prescribing; briefly, the available measures can be divided into medication assessment tools, and specific interventions to reduce inappropriate prescribing ^[29]. An overview is presented in table 1.

2.2.1. Medication assessment tools

As mentioned before, certain drugs are considered to be inappropriate for older patients, when the potential risks outweigh the potential benefits. These drugs are called potentially inappropriate medications (PIMs). Various lists of PIMs have been developed and used in studies investigating the appropriateness of prescribing in older patients. Some lists contain drugs to avoid in general, and some lists combine drugs with clinical data (e.g. certain drugs are considered inappropriate when a patient is suffering from a certain disease) ^[35]. These kind of medication assessment tools are called explicit criteria of inappropriate prescribing, i.e. consensus-based standards focusing on drugs and diseases.

One of the most frequently cited PIMs list is the list developed by Beers and co-workers, which has been updated twice and which was used in outpatient as well as inpatient studies for measuring and optimizing appropriateness of prescribing in older people ^[36-38]. Another approach was the development of criteria of overuse, misuse, and underuse for several drugs or diseases, amongst which the ACOVE criteria and the more recently developed STOPP / START criteria have received many attention ^[39;40].

Although lists of drugs to avoid and criteria for assessment of over-, mis- and underprescribing are valuable, they cannot replace individual clinical judgment for the purpose of medication review in older patients. Opposite to the explicit criteria of inappropriate prescribing, some medication assessment tools do not focus on specific drugs or diseases but on general criteria such as appropriate dosing, searching for drug-drug interactions, increasing compliance,... Using such an approach is called an implicit evaluation focusing on the patient and allowing differences between patients, and means in fact performing a medication review, by using a systematic approach. One of the methods that has undergone extensive reliability and validity testing is the Medication Appropriateness Index (MAI) ^[41], which was described by Hanlon and colleagues. In the original MAI, ten questions per drug taken are asked; these concern indication, effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration, and expense. The MAI has been used in various studies, as a measure for assessment of appropriateness of prescribing in older patients.

2.2.2. Interventions

Different types of interventions have been used in order to reduce inappropriate prescribing in older patients. These can roughly be categorized into educational interventions, computerized decision support systems, pharmacist-based interventions, and geriatric medicine services (the last one also for outpatients). The effects of these interventions have been studied, sometimes in a multi-faceted approach combining different techniques, and all types seem to have positive effects on appropriateness of prescribing.

2.3.

Clinical pharmacy

Over the last decades, the pharmacy profession has transitioned from a traditional drug-oriented perspective towards a patient-centered approach, which can be found in the concept of pharmaceutical care ^[42]. Pharmaceutical care is delivered by clinical pharmacists with the aim to improve outcomes and safety of drug therapy. Basically, the pharmaceutical care process consists of four steps, which are cyclic for an individual patient. These steps are pharmaceutical anamnesis, medication review, design of a pharmaceutical care plan, and follow up of this plan ^[43]. Although clinical pharmacists perform the pharmaceutical care process to manage the patient's drug therapy in every day clinical practice, the physician takes the ultimate responsibility for the care of the patient. Therefore, the clinical pharmacists work in close collaboration with physicians, nurses and other caregivers. Concerning older patients, optimization of drug therapy by clinical pharmacists is frequently investigated by assessment of the appropriateness of prescribing by using tools as previously described. Furthermore, the impact of clinical pharmacy can be measured by using process indicators, but it is clear that ~~the~~ studying the impact on clinical and economic endpoints is recommended ^[28;29].

3. Aim of this research and overview of the different chapters

The overall aim of this research was to evaluate the incidence and types of drug related problems occurring in older hospitalized patients, and to assess the role of the clinical pharmacist in their detection and prevention. In this dissertation, different aspects with regard to drug related problems in older inpatients are addressed, ranging from description of incidence and type of drug related problems, use of a particular drug class with a high risk for DRPs in older patients i.e. hypnotic drugs, towards a systematic approach for detection of drug related problems, and the role of the clinical pharmacist. An overview of the different studies is described hereafter, and the main research questions are detailed in table 2.

In Chapter 1 spontaneous reporting of adverse drug reactions (ADRs) as well as active observation by means of patient interviews is performed, in order to quantify the incidence of ADRs before and during hospital admission. This information is useful for raising the awareness of physicians and nurses about the burden and types of ADRs, and to gain insight in the drug classes most involved. Furthermore, it provides us information about the sources of reporting of ADRs.

Chapter 2 presents the incidence of drug related hospital admissions (DRHA) at the acute geriatric ward, in order to compare the results of this incidence with what has been found in previous studies performed in other countries. A broad definition of drug related problems including overuse and underuse is used. The appropriateness of drug therapy according to the well-known Beers' criteria (list of drugs to avoid in older patients) is explored. The results will also reflect which drugs most frequently cause a DRHA.

In Chapter 3 we describe the use of hypnosedative (HS) drugs at ten wards in our hospital, during two observation periods with a ten years interval. This drug class was chosen because use of HSs in older patients can impair both cognitive and movement function, with possible negative outcomes such as unwanted sedation, falls and fractures. The use of HSs is assessed by means of patient interviews, and by means of exploration of the pharmaceutical file. Additionally, the risk factors for use of hypnosedative drugs in our hospital are explored.

In Chapter 4 the ~~advices~~ recommendations of a clinical pharmacist are inventoried in terms of number and type, underlying drug related problems and acceptance rate by the treating physician. In addition, a panel of evaluators assessed the clinical impact of these ~~advices~~ recommendations, and rated their own acceptance. Also, MAI scores were calculated before and after the ~~advice~~ recommendation, in order to detect a potential increase in appropriateness of prescribing following the clinical pharmacist ~~advices~~ recommendations.

Finally in Chapter 5 a systematic approach for detection of drug related problems in older patients is evaluated. This is based on the Medication Appropriateness Index (MAI) scoring system, slightly

adapted and simplified for in-hospital use, and tested by two independent raters by evaluating the drug therapy at admission. In this study, we also want to evaluate if more inappropriate drug therapy would be associated with drug related hospital admissions.

Table 1: Tools for detection and prevention of drug related problems in older patients
(non exhaustive list)

MEDICATION ASSESSMENT TOOLS
1) Explicit criteria (drugs to avoid, drugs to avoid in certain diseases/syndromes, drugs to be used with caution)
<p>Beers (1991, updates 1997, 2003) McLeod (1997) ACOVE: Assessing Care of Vulnerable Elders (2001) IPET: Improved Prescribing in the Elderly Tool (2002) STOPP: Screening Tool of Older Person's Potentially inappropriate prescriptions (2008)</p> <p>DUE: Drug Use Evaluation (for specific drugs or drug classes) Criteria for justification of use, critical process indicators, complications, outcomes</p>
2) Implicit criteria
<p>MAI: Medication Appropriateness Index Indication, effectiveness, drug-disease interactions, dose, correct directions, correct directions practical for the patient, drug-drug interactions, duplication of therapy, duration, costs</p> <p>GMA: Geriatric Medication Algorithm Indication, risks, dose, interactions, complexity, compliance</p> <p>Lipton's criteria Drug allergy, dosage, drug schedule, contraindication/indication, drug-drug interaction, duplication</p>
INTERVENTIONS
<p>Educational interventions Teaching, interactive workshops, provision of decision algorithms, face-to-face visits</p> <p>Computerized support systems Decision support for physicians Alerts for pharmacists</p> <p>Pharmacist-based interventions Medication review, recommendation letters, consultant pharmacist</p> <p>Geriatric medicine services Multidisciplinary geriatric team (geriatrician, nurse specialist,...); inpatients and outpatients</p>

Table 2: Overview of chapters and main research questions

Chapter	Focus	Main research questions	Period, setting	Number of patients
Chapter 1	Reporting adverse drug reactions (ADRs)	<ul style="list-style-type: none"> - What is the incidence of ADRs before and during hospital admission? - Which are the differences between spontaneous reporting and patient interview concerning number and types of ADRs reported? - Which drugs or drug classes cause ADRs in older patients admitted to the geriatric ward? 	8 months geriatric ward	168 patients involved 56 patients interviewed
Chapter 2	Drug related hospital admissions (DRHA)	<ul style="list-style-type: none"> - What is the incidence of DRHA looking at overuse and misuse and what are the most common underlying drug related problems? - Which drugs or drug classes are most frequently involved? - Is the incidence of DRHA comparable to other studies? - Is there a relationship between DRHA and drugs listed by Beers (drugs to avoid in older patients) - Is there a relationship between DRHA and intake of a higher number of drugs? 	3 non consecutive months geriatric ward	110 patients
Chapter 3	Hyposedative (HS) drug use	<ul style="list-style-type: none"> - What is the prevalence of HS use in our hospital, before and during admission? - For how many patients HS use is discontinued in the hospital and how many patients are started on HS during admission? - What are the risk factors for HS use (e.g. age)? - What is the evolution with a similar observation 10 years ago? 	6 weeks 10 hospital wards (excl geriatric ward)	326 patients
Chapter 4	Clinical pharmacist recommendations	<ul style="list-style-type: none"> - How many and which recommendations are provided by the clinical pharmacist? - What is the acceptance rate by the treating physician and by a panel of 4 evaluators? - What is the clinical relevance of the recommendations assessed by this panel and how is the inter-rater agreement? - Is there a change in appropriateness of prescribing before and after the accepted recommendations (using the Medication Appropriateness Index)? 	4 month period geriatric ward	100 patients
Chapter 5	Adapted Medication Appropriateness Index (MAI)	<ul style="list-style-type: none"> - Is an adapted version of the MAI index applicable and what are the results per question? - What is the inter-rater agreement between a clinical pharmacist and a geriatrician? - Is there a relationship with DRHA and a more inappropriate adapted MAI score? 	geriatric ward	50 patients

4. References

1. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm* 1990;47:533-543.
2. Hallas J, Harvald B, Gram LF et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med* 1990;228:83-90.
3. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 2002;24:46-54.
4. Cunningham G, Dodd TR, Grant DJ et al. Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment. *Age Ageing* 1997;26:375-382.
5. Mannesse CK, Derkx FH, de Ridder MA et al. Contribution of adverse drug reactions to hospital admission of older patients. *Age Ageing* 2000;29:35-39.
6. Nelson KM, Talbert RL. Drug-related hospital admissions. *Pharmacotherapy* 1996;16:701-707.
7. Hallas J, Worm J, Beck-Nielsen J et al. Drug related events and drug utilization in patients admitted to a geriatric hospital department. *Dan Med Bull* 1991;38:417-420.
8. 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;50:1962-1968.
9. Pirmohamed M, James S, Meakin S et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-19.
10. Kaiser RM, Schmader KE, Pieper CF et al. Therapeutic failure-related hospitalisations in the frail elderly. *Drugs Aging* 2006;23:579-586.
11. Anonymous. International monitoring of adverse reactions to drugs. Adverse reaction terminology. Uppsala: WHO Collaborating Centre for International Drug Monitoring. 1995.
12. Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. *J Clin Pharm Ther* 2007;32:113-121.
13. Lindley CM, Tully MP, Paramsothy V et al. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. *Age Ageing* 1992;21:294-300.
14. Passarelli MC, Jacob-Filho W, Figueras A. Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. *Drugs Aging* 2005;22:767-777.
15. van den Bemt PM, Egberts AC, Lenderink AW et al. Risk factors for the development of adverse drug events in hospitalized patients. *Pharm World Sci* 2000;22:62-66.
16. Hajjar ER, Hanlon JT, Artz MB et al. Adverse drug reaction risk factors in older outpatients. *Am J Geriatr Pharmacother* 2003;1:82-89.
17. Field TS, Gurwitz JH, Avorn J et al. Risk factors for adverse drug events among nursing home residents. *Arch Intern Med* 2001;161:1629-1634.
18. Field TS, Gurwitz JH, Harrold LR et al. Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc* 2004;52:1349-1354.

19. Lund BC, Carnahan RM, Egge JA et al. Inappropriate prescribing predicts adverse drug events in older adults. *Ann Pharmacother* 2010;44:957-963.
20. Steinman MA, Landefeld CS, Rosenthal GE et al. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006;54:1516-1523.
21. Page RL, Linnebur SA, Bryant LL et al. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. *Clin Interv Aging* 2010;5:75-87.
22. Swift CG. The clinical pharmacology of ageing. *Br J Clin Pharmacol* 2003;56:249-253.
23. Schwartz JB. The current state of knowledge on age, sex, and their interactions on clinical pharmacology. *Clin Pharmacol Ther* 2007;82:87-96.
24. Le Couteur DG, Hilmer SN, Glasgow N et al. Prescribing in older people. *Aust Fam Physician* 2004;33:777-781.
25. Batty GM, Grant RL, Aggarwal R et al. Using prescribing indicators to measure the quality of prescribing to elderly medical in-patients. *Age Ageing* 2003;32:292-298.
26. Hanlon JT, Artz MB, Pieper CF et al. Inappropriate medication use among frail elderly inpatients. *Ann Pharmacother* 2004;38:9-14.
27. Suggested definitions and relationships among medication misadventures, medication errors, adverse drug events, and adverse drug reactions *Am J Health Syst Pharm* 1998;55:165-166.
28. Spinewine A, Schmader KE, Barber N et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet* 2007;370:173-184.
29. Kaur S, Mitchell G, Vitetta L et al. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. *Drugs Aging* 2009;26:1013-1028.
30. Classen DC, Pestotnik SL, Evans RS et al. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1997;277:301-306.
31. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200-1205.
32. Jha AK, Kuperman GJ, Teich JM et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc* 1998;5:305-314.
33. Eland IA, Belton KJ, van Grootheest AC et al. Attitudinal survey of voluntary reporting of adverse drug reactions. *Br J Clin Pharmacol* 1999;48:623-627.
34. Leendertse AJ, Egberts AC, Stoker LJ et al. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008;168:1890-1896.
35. Shelton PS, Fritsch MA, Scott MA. Assessing medication appropriateness in the elderly: a review of available measures. *Drugs Aging* 2000;16:437-450.
36. Beers MH, Ouslander JG, Rollinger I et al. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med* 1991;151:1825-1832.
37. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997;157:1531-1536.
38. Fick DM, Cooper JW, Wade WE et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 2003;163:2716-2724.

39. Wenger NS, Shekelle PG. Assessing care of vulnerable elders: ACOVE project overview. *Ann Intern Med* 2001;135:642-646.
40. Gallagher P, Ryan C, Byrne S et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther* 2008;46:72-83.
41. Hanlon JT, Schmader KE, Samsa GP et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992;45:1045-1051.
42. Berenguer B, La CC, de la Matta MJ et al. Pharmaceutical care: past, present and future. *Curr Pharm Des* 2004;10:3931-3946.
43. Cipolle R, Strand LM, Morley PC. *Pharmaceutical Care Practice*. New York. Mc Graw Hill. 1998.

Chapter 1: Reporting Adverse Drug Reactions on a Geriatric Ward: a Pilot Project

This chapter is based upon:

Somers A, Petrovic M, Robays H, Bogaert M. Reporting adverse drug reactions in a university hospital: a pilot project on a geriatric ward. Eur J Clin Pharmacol 2003, 58: 707-714.

ABSTRACT

Objective:

To test a method for registration of adverse drug reactions (ADRs) resulting in hospital admission and of ADRs occurring during hospital stay. Spontaneous reporting was compared with data from patient interview.

Methods:

Spontaneous reporting of ADRs by nurses and physicians, as well as patient interviews by pharmacists. This pilot project was carried out in the geriatric ward of the Ghent University Hospital during 8 months, in order to develop suitable registration forms and to test feasibility. Causality, severity, type and level of intervention of the reported ADRs were analysed. Reports from physicians and nurses were compared with the data obtained by patient interviews.

Results:

During the 8 months, for 168 patients 12 spontaneous reports were received from physicians and nurses. Fifty-six of these patients were interviewed and 32 ADRs were reported. Only two ADRs detected by patient interview were also reported spontaneously. The interviews of the 56 geriatric patients indicated that 20% of them were admitted to the hospital because of an adverse drug reaction. ADRs occurred during hospital stay in another 20% of those patients.

Conclusion:

Spontaneous reporting of ADRs by physicians and nurses revealed considerably less ADRs than patient interview by pharmacists. Physicians and nurses however reported the more serious adverse drug reactions that occurred during hospital stay, whereas the interviews revealed more ADRs that caused hospital admission. Our data confirm that ADRs are an important cause of hospital admission of geriatric patients, and occur frequently during their hospital stay.

Keywords:

Adverse drug events (ADE), adverse drug reactions (ADR), patient interview, pharmacovigilance, spontaneous reporting

INTRODUCTION

Adverse drug reactions (ADRs) are a frequent cause for hospitalization and occur often in hospitalised patients ^[1-5]. However, the frequency of ADRs leading to hospital admission or occurring during hospital stay differs markedly from study to study ^[6]. This is probably due in part to the use of different definitions for adverse drug reactions ^[7]. According to the WHO definition, an ADR is “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function”. Some authors report in fact adverse drug events (ADEs), in accordance with the WHO definition “any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment”. Other authors include in their definition of ADRs also medication errors, which are preventable events leading to inappropriate medication use or patient harm.

The variation in reported incidence of ADRs can also be explained by different methods of investigation. Some studies involve only spontaneous reporting while others use active monitoring systems. Moreover, there are differences between stimulated versus non-stimulated reporting systems, as well as between manual and electronic active monitoring systems.

In our country a national ADR reporting system exists, organised by the Belgian Centre for Pharmacovigilance. However, data show that the number of reports coming from hospital staff members is quite low ^[8]. In order to test the detection rate and the applicability of the methods, we compared the results of spontaneous reporting and of active observation of ADRs in the geriatric ward of our university hospital.

METHODS

Setting and study design

The Drug and Therapeutics Committee of our hospital initiated the study. In Belgium, such a committee is in charge of developing the hospital formulary, formulating the procedures of drug

handling, inspecting the drug distribution system and analysing the drug consumption. This prospective study was conducted in 1999, from March 26 until November 24, in the geriatric ward of the Ghent University Hospital (27 beds). ADRs were collected by spontaneous reporting by nurses and physicians, and by interview of patients. Before the interview, the patients received an information sheet and gave written informed consent. The institutional Ethics Committee approved the study.

Population and sampling

Spontaneous reporting of ADRs was possible for all patients admitted to the geriatric ward (27 beds) during the study period. For patient interview however, not all patients were eligible; exclusion criteria were dementia or confusion, severe illness, short hospital admission (< 3 days) and refusal of the patient to participate. The aim was to interview all patients who were not excluded.

Definition and classification of adverse drug reactions

We defined an ADR according to the WHO, including only adverse events presumed at the moment of reporting to be related to a drug treatment. This does not exclude that some events were categorized as “not related to the treatment” after causality assessment.

The ADRs were classified according to the reporter (nurse, physician, interviewer or patient). For every ADR, causality, severity and type were assessed in accordance with the WHO criteria ^[9]. In addition, the level of intervention was attributed, using a six level scale (appendix 1: registration form). Each ADR was also classified according to the system-organ class. The drugs involved were classified according to the ATC (Anatomical Therapeutical and Chemical) classification ^[10], the route of administration and the whether the drugs had been taken at home or started in the hospital.

Spontaneous reporting by nurses and physicians

We developed a registration form (appendix 1) based on the form used by the Belgian Centre for Pharmacovigilance. Additionally, in our study, the level of intervention, the causality and the person who drew the attention to the adverse event were reported.

Before the study was started, the registration sheet was tested several times by a physician working on the geriatric ward. This was done to evaluate whether there were no relevant questions missing, whether the questions were clear, and whether the time to complete a registration form was not too long. The physicians and nurses of the geriatric ward were then informed about the definition of ADRs and received instructions about the method of reporting. The registration sheet was explained, and the nurses and physicians were asked to report all adverse events (both serious and non-serious), for which they presumed causality with one of the drugs taken. All report forms were sent to the pharmacy and were discussed weekly with the physicians.

Patient interview

Two hospital pharmacists questioned the patients about ADRs. They were chosen as neutral interviewers independently from physicians and nurses as spontaneous reporters.

A special form was designed (appendix 2), to register patient data, disease state(s), reason(s) for hospitalization and use of medication, both at home and in the hospital. The interviewers completed this part of the form before interviewing the patient, because it gave them the opportunity to interview the patients in function of their drug use. The interview took place in three steps. First, the patients were asked a standard open question, i.e. whether they had experienced an ADR. If so, the ADR was noted. The patients were then asked about complaints concerning the different organ systems; these questions helped the patients to recall ADRs. Finally, the patients were asked for adverse events in function of their medication use.

The two pharmacists conducted the first six interviews together, in order to evaluate the registration form and to assure reliability between the interviewers. Furthermore, a person working at the National Centre for Pharmacovigilance accompanied an interviewer during two interviews, in order to validate the questions and the information recorded. To avoid interviewers' bias the

pharmacists exchanged all the information retrieved at each interview and worked together on data entry and data analysis.

For all complaints mentioned, the interviewers asked questions about which drug the patient suspected, the time relationship and how the patient got information about the ADR (physician, medication leaflet...). All adverse drug reactions mentioned were reported on a special form, even if the interviewer had doubts about the causality. Complaints which the patient did not link to a specific drug were also registered if the interviewer suspected causality.

Data validity and causality assessment

All report forms (both from the spontaneous reporting and from the patient interview) were weekly discussed with the physicians in order to validate the data collected and to assess causality, severity and type, and level of intervention. No formal causality assessment was made. For spontaneous reported ADRs the relationship between the complaint and a drug was indicated by the reporter. For reports based on patient interview the causality was discussed by the interviewer and the treating physician. During this discussion, the time relation and the information about adverse events on the scientific medication leaflet of a specific drug were taken into account. Furthermore, the causality of all cases was discussed within a group consisting of a clinical pharmacologist, a person of the Belgian Center for Pharmacovigilance, a geriatrician and the pharmacist interviewers.

Data analysis

The adverse drug reactions detected by spontaneous reporting and by patient interview were compared for rate, severity and drugs involved (descriptive analysis). The ADRs reported by patient interview were analysed using the Statistical Package of Social Sciences (SPSS 10.0). A Mann-Whitney test was used for assessing differences in age, number of prescribed drugs and length of stay between patients for whom an ADR or a serious ADR was reported or those for whom this was not reported. We also looked whether gender or pharmacological class of drugs taken had an influence to the occurrence of an ADR or a serious ADR by using the Pearson Chi-Square (X^2) test.

RESULTS

During the eight-month study period, 168 patients were admitted to the geriatric ward, resulting in 5279 days of observation. The demographic data of these patients are presented in Table 1. The median length of stay for these patients was 16 days (3 – 61, mean 31.4). The average length of stay was heavily influenced by the fact that some patients were hospitalised for more than two months.

a) Spontaneous reporting by nurses and physicians

An ADR report was received for 12 of the 168 hospitalised patients. Physicians reported 8 of them, nurses 4. Six reports concerned medication taken already at home and continued during hospitalization, and 6 concerned medication started in hospital. The ADRs concerned cardiovascular medication (4), central nervous system medication (4), antibiotics (1), analgesics (1), antihistaminics (1) and antidiabetics (1). Eleven drugs were taken orally, and 1 drug was administered dermally.

With regard to causality, 9 events were interpreted as “probably” related to a drug, and 3 as “possibly” related. Six ADRs were classified as “serious” and caused hospital admission or prolonged hospital stay. For one ADR the attributed level of intervention was one (no change in dose), for eight ADRs the intervention level was two (drug was stopped), and for three ADRs the intervention level was three (drug was stopped and additional therapy was required). All reported ADRs were type A reactions, none were idiosyncratic. Details of the reports are given in Table 2.

b) Patient interview

From the 168 patients, 69 met the inclusion criteria for an interview, but only 56 of these patients could be interviewed, due to practical problems. The general characteristics of the 56 interviewed patients are shown in Table 1. Their mean age was 80.1 years (62 – 94); 37 patients were female, 19 male. The average number of drugs taken at the moment of interview was 8.7 (3 – 16, median 9). There were no major differences between men and women in regard to these parameters. Statistical analysis showed no correlation between age, gender and length of stay or number of drugs taken on the one hand, and the occurrence of ADRs or serious ADRs on the other hand.

A total of 32 ADRs that occurred in 23 patients, were reported. The causality of these ADRs was defined as “probable” or “possible”, never as “definite”, “improbable” or “unclassifiable”. The classification of the ADRs by system-organ class is described in Table 3. ADRs were reported for cardiovascular medication (10), respiratory medication (7), central nervous system medication (5), and others (10). They concerned mostly orally administered drugs (n=28), 11 started at home and not continued in the hospital and 21 continued or started in the hospital.

Statistical analysis showed a correlation between the intake of respiratory medication and the development of an adverse drug reaction ($p=0.008$; $\chi^2=15.543$). Three patients developed oedema, one patient developed osteoporosis and one patient developed oedema and osteoporosis as a consequence of the intake of oral corticoids as treatment for COPD. These complaints were all linked with oral corticosteroids by the patients, because their general practitioner or another physician had informed them. A correlation was also found between taking central nervous system drugs and the development of a serious adverse drug reaction ($p=0.046$; $\chi^2=11.262$). Four of them were falls in patients on hypnotics.

The results of the analysis of the 32 ADRs are given in Table 4. For 15 ADRs (47%), the patient suspected a relationship with a drug; for 17 reports (53%) causality was presumed by the interviewer and not by the patient. Patients always mentioned the physician as information source for their suspicion of a relationship between the symptoms and the drug. Causality was defined as “probable” for 23 (72%) reports, and as “possible” for 9 (28%) reports. Twelve ADRs (38%) were classified as serious, 11 of these causing hospital admission and one causing prolonged hospital stay. These concerned mostly falls and electrolyte disorders. All ADRs reported were type A reactions. Only two of the ADRs detected by the interviewers were also reported spontaneously by nurses.

DISCUSSION

Number and nature of the reports

That only 12 spontaneous reports were given for 168 patients was unexpected, and was considered as a poor result in comparison with the number of ADRs reported at the patient

interview. Although it is generally recognized that only a small proportion of ADRs is spontaneously reported ^[11], we expected to have more reports because the aim and method of the study system was extensively explained in advance to the nurses and physicians. Other studies found that the reporting rate can be increased by a so-called stimulated spontaneous reporting system ^[12-14].

For this low number, several possible explanations can be found. It could be that the physicians and nurses underreported ADRs due to their very high administrative workload. Perhaps they underestimated the occurrence of ADRs perhaps due to the absence of systematic stimulation of spontaneous reporting. It is also possible that physicians and nurses focused on ADRs occurring during hospital treatment, as they never reported ADRs causing hospital admission. Finally, there may have been a hesitation to report ADRs that were preventable.

Table 1 shows that the mean age of the interviewed patients was higher than the mean age of all patients admitted to the geriatric ward during the study period (the median age is comparable). Furthermore, the mean length of hospital stay of the subgroup of interviewed patients is comparable to that for all patients admitted to the geriatric ward, but the median length of stay is much lower (14.0 days versus 31.4 days).

Adverse drug reactions occurred in 41% of the interviewed patients. In 20% of them, the ADR was considered to be serious, requiring almost always hospital admission. Another 20% of the patients showed a less serious adverse drug reaction, leading to treatment interruption in half of the cases. These incidence data for ADRs are higher than those reported in other studies, in which it has been estimated that ADRs were present in 10 to 30% of hospitalised patients ^[1-4]. In the meta-analysis of Lazarou et al ^[6], an incidence of 10.9% was found for patients experiencing an ADR during their hospital stay, and incidence of 15.1% for both ADRs causing hospital admission and occurring during hospital stay.

Several reasons can explain the high incidence found in our study. We included first of all also “possible” ADRs, while Lazarou et al ^[6] included only “definite” and “probable” ADRs. Since we classified nine of the reported ADRs as having a possible causal relationship with a drug, it is possible that a number of false positives were included ^[15,16]. This remains unclear since no additional efforts were made to detect causes for the complaints other than drugs. However, no change in therapy was needed for these complaints. Nevertheless, the incidence of 20% of

patients hospitalised because of an ADR remains high. Secondly, in our study, patient interview was intensive, since the patients were also asked about ADRs in function of their medication profile. Thirdly, we studied a geriatric population, which could be more sensitive to ADRs. However, age as a risk factor for adverse drug reactions is a controversial issue ^[17-19]. A recent study even found an inverse relationship between age and adverse events for ADRs occurring during hospital stay ^[4]. In our study the geriatric patients studied took a high number of drugs, which is a well-known risk factor for developing adverse drug reactions ^[2,4,17,18,20].

Method

Some general remarks about the methods used can be made. The main limitation of this study consists in the limited number of patients observed. Although the study was conducted during eight months, we had some practical problems for interviewing the patients due to short hospitalizations and due to changes in physician staff, which led to difficulties for inclusion of patients. Furthermore, it was chosen to conduct this study at one single ward due to time limitations.

Secondly, the selection for the interview excluded the sickest and most confused patients. The median length of stay of the interviewed patients was much lower than the median length of stay of all hospitalised patients. Probably, more adverse drug reactions could have occurred in the non-interviewed patients.

Finally, we did not apply a formal causality assessment e.g. with a scoring system as developed by Naranjo et al. ^[21], and spontaneous reporting was only partially and unequally stimulated. Despite these methodological pitfalls, we consider this study valuable since it gave us the opportunity to test the methods of spontaneous ADR reporting and of patient interview, to test the registration forms, to assess roughly the incidence and type of ADRs in the patients admitted to our geriatric ward, and to increase the general awareness about undesirable drug effects.

Our results show a large difference between the number of ADRs reported spontaneously and those identified by patient interview. Spontaneous reporting by physicians and nurses yielded relatively more adverse effects for medication taken in hospital, and relatively more events with a higher severity. These findings are similar to those of van den Bemt et al ^[12] who compared physicians, nurses and patients as sources of ADR reports.

Many studies have compared intensive surveillance programs with spontaneous reporting programs. The results show an important under-reporting of adverse reactions in spontaneous reporting systems [3,13,16,22,23]. Spontaneous reporting must be continuously stimulated. This can be achieved by an adverse drug reaction committee, which collects the ADR reports and gives feedback to the hospital personnel [14]. In our study, the spontaneous reporting of ADRs by nurses and physicians was not stimulated continuously. The protocol was explained to the physicians and nurses involved before the start of the study, but the interviewers did not ask them systematically about the occurrence of ADRs. On the other hand, a patient interview such as that performed in this study is difficult to maintain on a continuous basis, because of the high personnel investment. In our study, the interviewers spent on average three hours per week for patient interviews, and one hour per week for data analysis. The time investment per patient was on average one hour and a half, including preparation of the interview, the interview itself, the discussion with the treating physician and the data analysis. Intermittent patient interview on different wards could be a valuable alternative, combined with a central ADR reporting system in the hospital.

Further actions

The relatively high incidence of adverse drug reactions observed in the studied geriatric population was extensively discussed in the Drug and Therapeutics Committee. The first action taken consisted of increasing the awareness of the ADR problem throughout our hospital. Therefore, the results of the study were presented to the nurses and physicians of the geriatric ward, and a special session about undesirable effects of drugs was introduced into the nurse training program of our hospital.

Our Drug and Therapeutics Committee decided that further investigations are necessary for estimation of the incidence and type of ADRs in our hospital. A first study will consist of exploring possible relationships between drug profile and readmission on the geriatric ward, by analysing the medication profiles of the admitted geriatric patients in terms of risk for non compliance and ADR problems. In addition, a study with the same methodology will be carried out on other wards to investigate whether the burden of ADRs is similar in other vulnerable patients. At last, a central

ADR reporting point will be set up in our hospital, after an intensive information campaign and with continuous feedback to the health care practitioners, via the hospital drug bulletin.

CONCLUSION

The results of this study confirm that adverse drug reactions represent an important problem in the geriatric population. Using a combination of spontaneous reporting and interview of patients seems useful for examining the occurrence of adverse drug reactions. Although remarks can be made about the methodology applied, we consider this study to be useful for its educational contribution in our hospital. Since continuous patient interview in our institution is not possible in terms of personnel investment, we will focus on stimulated spontaneous reporting and intermittent patient interview in different hospital wards. These actions will be carried out to increase the awareness about adverse drug reactions and to find pathways to decrease their occurrence.

ACKNOWLEDGEMENTS

The authors are indebted to the participating hospital pharmacists (M. Van Hooreweghe, V. De Smet, F. Buyle, E. Kestens), Professor M. Afschrift, Professor D. Pevernagie, Head Nurse H. Van Doninck, the nursing staff and the patients of the geriatric ward for their contribution to this study.

TABLES

Table 1: Demographic data of the geriatric patients admitted during the study period (n=168), of the interviewed patients (n = 56) and of the patients in whom an ADR was reported (=13 females patients and 10 male patients)

Geriatric patients admitted during the study period (n = 168)	Mean	Median	Range
Age (years)	75.1	79	62 - 97
Length of hospital stay (days)	16.2	31.4	7 – 61
Interviewed patients (n = 56)	Mean	Median	Range
Age (years)	80.1	80.0	62 – 94
Length of hospital stay (days)	18.6	14.0	4 – 61
Number of drugs taken at the moment of interview for patients with ADR (n=23)	9.3	8.0	6 – 16
Number of drugs taken at the moment of interview for patients without ADR (n=33)	8.3	9.0	3 – 14
Interviewed female patients for whom an ADR was reported (n = 13)	Mean	Median	Range
Age (years)	78	77	70 - 86
Length of hospital stay (days)	17.2	13.9	4 – 39
Number of drugs taken at the moment of interview	10.5	11	8 –13
Interviewed male patients for whom an ADR was reported (n = 10)	Mean	Median	Range
Age (years)	79	79	62 – 94
Length of hospital stay (days)	18.9	14.6	6 – 61
Number of drugs taken at the moment of interview	10.2	8	3 – 16

Table 2: Adverse drug reactions reported spontaneously by physicians and nurses

Nr	Reported by	Age	M/F	Drug	Route	Home / hospital (*)	Symptoms	Causality	Level	SADR (**)	Type
1	Physician	77	F	Lormetazepam	Oral	Home	Pre-delirium	Probable	3	Yes	A
2	Physician	75	F	Lisinopril	Oral	Home	Hyperkalaemia	Probable	2	Yes	A
3	Nurse	82	F	Nitroglycerine	Dermal	Hospital	Hypotension	Probable	2	No	A
4	Physician	83	F	Amoxyclav	Oral	Hospital	Diarrhoea	Probable	2	No	A
5	Nurse	68	M	Haloperidol	Oral	Home	Sleep apnoea	Possible	1	No	A
6	Nurse	78	F	Cetirizine	Oral	Hospital	Dizziness, sleepiness	Probable	2	No	A
7	Physician	81	M	Furosemide, spironolactone	Oral	Home	Hyponatraemia	Probable	3	Yes	A
8	Physician	86	F	Insulin, metformine	Sc, oral	Home	Hypoglycaemia	Probable	3	Yes	A
9	Physician	83	F	Citalopram	Oral	Hospital	Hypotension	Possible	2	No	A
10	Physician	80	F	Citalopram	Oral	Hospital	Hypotension	Possible	2	No	A
11	Nurse	77	F	Tamoxifen	Oral	Hospital	Nausea, vomiting	Probable	2	Yes	A
12	Physician	82	M	Spironolactone	Oral	Home	Hyperkalaemia	Probable	2	Yes	A

(*): Home: drug started at home; hospital: drug started in the hospital

(**): SADR: Serious Adverse Drug Reaction

Table 3: Classification of the possible and probable ADRs reported by patient interview (n = 32) by system-organ class

System-organ class	Number of ADRs (%)
Bone & muscle disorders	6 (19%)
Respiratory disorders	5 (16%)
Gastro-intestinal disorders	5 (16%)
Central nervous system disorders	5 (16%)
Other	5 (16%)
Cardiovascular disorders	3 (9%)
Psychiatric disorders	2 (6%)
Skin disorders	1 (3%)

Table 4: Classification of the adverse drug reactions reported after patient interview

Characteristic of ADE	Number of ADRs (%)
Reports per gender	
- Male	10 (43%)
- Female	13 (57%)
Causality	
- Probable	23 (72%)
- Possible	9 (28%)
Causality presumed by	
- Patient or patient + interviewer	15 (47%)
- Interviewer only	17 (53%)
Level	
- Level 1 (no change in dose)	13 (41%)
- Level 2 (dose changed or drug stopped)	12 (38%)
- Level 3 (drug stopped + additional therapy)	7 (22%)
Severity	
- Serious ADR (hospital admission, prolonged length of stay)	12 (38%)
- Non serious ADR	20 (62%)
Type	
- Type A	32 (100%)
- Type B	0 (0%)
Relation with spontaneous reports	
- Reported spontaneously and after patient interview	2 (6%)
- Only reported after patient interview	30 (94%)

REFERENCES

1. Classen DC, Pestotnik SL, Evans RS et al (1997) Adverse drug reactions in hospitalised patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 277(4): 301-6
2. Lagnaoui R, Moore N, Fach J et al (2000) Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *Eur J Clin Pharmacol* 56 (2): 181-6.
3. Dormann H, Muth-Selbach U, Krebs B et al (2000) Incidence and costs of adverse drug reactions during hospital. *Drug Saf* 22 (2): 161-168.
4. Moore N, Lecointre D, Nobelt C, Mabile M (1998). Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol* 45: 301-8.
5. Levy M, Azaz-Livshits T, Sadan B et al (1999) Computerized surveillance of adverse drug reactions in hospital: implementation. *Eur J Clin Pharmacol* 54(11): 887-92.
6. Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of adverse drug reactions in hospitalised patients. A meta-analysis of prospective studies. *JAMA* 279: 1200-05.
7. American Society of Health-System Pharmacists (1998) Suggested definitions and relationships among medication misadventures, medication errors, adverse drug reactions and adverse drug reactions. *Am J Health Syst Pharm* 55: 165-166.
8. Belgian Center for Pharmacovigilance: The monitoring of adverse drug reactions in Belgium 1995-1996. Report of April 1997. Unpublished data.
9. Anonymous (1995) International monitoring of adverse reactions to drugs. Adverse reaction terminology. Uppsala: WHO Collaborating Centre for International Drug Monitoring.
10. Anonymous (1994) Anatomical Therapeutic Chemical (ATC) classification index. Oslo: WHO Collaborating Centre for Drug Statistics Methodology.
11. Thurmann PA (2001) Methods and systems to detect adverse drug reactions in hospitals. *Drug Saf* 24 (13): 961-8.
12. van den Bemt PMLA, Egberts ACG (1999) Adverse drug events in hospitalised patients. A comparison of physicians, nurses and patients as sources of reports. *Eur J Clin Pharmacol* 55: 155-158.
13. Smith CC, Bennett PM, Pearce HM et al (1996) Adverse reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. *Br J Clin Pharmacol* 42: 423-429.
14. Etzel JV, Brocavich JM, Rousseau M (1995) Impact of the development of a multidisciplinary adverse drug reaction committee. *Hosp Pharm* 30: 1083-1087.

15. Mitchell AS, Henry DA, Sanson-Fischer R et al (1988) Patients as a direct source of information on adverse drug events. *BMJ* 297: 891-893.
16. Egberts ACG, Smulders M, De Koning GHP et al (1996) Can adverse drug reactions be detected earlier? A comparison of reports by patients and professionals *BMJ* 313: 530-1.
17. Hoigne R, Lawson DH, Weber E (1990) Risk factors for adverse drug reactions - epidemiological approaches. *Eur J Clin Pharmacol* 39(4): 321-5.
18. Gurwitz JH, Avorn J (1991) The ambiguous relation between aging and adverse drug reactions. *Ann Intern Med* 114: 956-66.
19. Carbonin P, Pahor M, Bernabei R, Sgadari A (1991) Is age an independent risk factor of adverse drug reactions in hospitalised medical patients? *J Am Geriatric Soc* 39(11): 1093-9.
20. Van den Bemt PMLA, Egberts ACG, Lenderink AW et al (2000) Risk factors for the development of adverse drug events in hospitalised patients. *Pharm World Sci* 22: 62-66.
21. Naranjo CA, Busto U, Sillers Em, et al (1981) A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30: 239-245.
22. Jha AK, Kuperman GJ, Teich JM et al (1998) Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Inform Assoc* 1998 5 (3):305-14
23. Eland IA, Belton KJ, van Grootheest AC et al (1999) Attitudinal survey of voluntary reporting of adverse drug reactions. *Br J Clin Pharmacol* 48 (4): 623-7.

APPENDICES

Appendix 1: Registration sheet for spontaneous reporting of ADRs

PATIENT DATA Patient name or initials: 0 M 0 F Date of birth: Date of admission:/...../..... Date of registration:/...../..... Reason for admission: Other medical details: Known allergies:																																									
ADVERSE EVENT Symptoms, course and treatment: Event was or resulted in: <input type="checkbox"/> Life-threatening <input type="checkbox"/> Permanent or significant disability <input type="checkbox"/> Hospitalization or prolonged hospitalization <input type="checkbox"/> None of the above Date of onset:/...../..... End date:/...../..... Patient outcome: <u>Level of intervention</u> <input type="checkbox"/> Level 1 No change in treatment <input type="checkbox"/> Level 2 Dose adjustment or drug stopped, no additional treatment required <input type="checkbox"/> Level 3 Dose adjustment or drug stopped, other treatment required <input type="checkbox"/> Level 4 Transfer to intensive care setting <input type="checkbox"/> Level 5 ADE caused permanent harm to the patient <input type="checkbox"/> Level 6 ADE either directly or indirectly led to the patient's death																																									
PHARMACOTHERAPY Suspected drug																																									
<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th style="width: 20%;">Drug name</th> <th style="width: 10%;">Dose</th> <th style="width: 10%;">Form</th> <th style="width: 10%;">Route</th> <th style="width: 30%;">Indication</th> <th style="width: 10%;">Start</th> <th style="width: 10%;">Stop</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>							Drug name	Dose	Form	Route	Indication	Start	Stop																												
Drug name	Dose	Form	Route	Indication	Start	Stop																																			
Causality assessment: <input type="checkbox"/> definite <input type="checkbox"/> probable <input type="checkbox"/> possible <input type="checkbox"/> improbable Can you indicate something that can explain the adverse drug event? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, what?																																									
<u>Other drugs:</u>																																									
<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th style="width: 20%;">Drug name</th> <th style="width: 10%;">Dose</th> <th style="width: 10%;">Form</th> <th style="width: 10%;">Route</th> <th style="width: 30%;">Indication</th> <th style="width: 10%;">Start</th> <th style="width: 10%;">Stop</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>							Drug name	Dose	Form	Route	Indication	Start	Stop																												
Drug name	Dose	Form	Route	Indication	Start	Stop																																			
TESTS / LABORATORY DATA (only if relevant, please attach copies) Blood tests: Drug levels:																																									
REPORTER Name: (please fill in your name, in order to provide feedback) Adverse event indicated by: <input type="checkbox"/> Physician <input type="checkbox"/> Nurse <input type="checkbox"/> Patient <input type="checkbox"/> Family <input type="checkbox"/> Pharmacist Can this report be sent to the National Centre for Pharmacovigilance? <input type="checkbox"/> Yes <input type="checkbox"/> No																																									

Appendix 2: Questionnaire for patient interview

1. Open questions

Did you take drugs at home? 0 Yes 0 No If yes, which drugs:

Did you have complaints about these drugs? 0 Yes 0 No

If yes, which complaints: since

Which drugs do you think caused these complaints?

How long did you take these drugs?

Where do you got the information about the relationship with the drug?

Did you have these complaints before you used these medicines? 0 Yes 0 No 0 Unknown

Can you suggest other causes for the complaints, besides the drugs you took at home?

Do you get drugs in the hospital? 0 Yes 0 No

Do you have complaints about these drugs? 0 Yes 0 No

2. Questions concerning the different organ systems

Do you have complaints about:

	which complaints?	since?	suspected drug?	source? P/Ph (*)
0 skin, hair, nails
0 muscles
0 joints, bones
0 face, head
0 eyes, visibility
0 hearing, odor, taste
0 throat, voice
0 airways
0 heart, blood circulation
0 stomach, digestion
0 kidneys, urinary tract
0 sleeping
0 nervous system
0 mental condition
0 other complaints

(*): P = physician; Ph = pharmacist

3. Specific questions in view of the drug list

Have you experienced the following adverse events?

.....

Did you have these complaints before you used these medicines? 0 Yes 0 No 0 Unknown

Can you suggest other causes for the complaints, besides the drugs you took at home?

Chapter 2: Contribution of drug related problems to hospital admission in the elderly

This chapter is based upon:

Somers A, Robays H, Vander Stichele R, Bogaert M, Petrovic M. Contribution of drug related problems to hospital admission in the elderly. J Nutr Health Aging 2010;14:477-82

ABSTRACT

Purpose:

To investigate the frequency and type of drug related problems (DRPs) in geriatric patients (> 65 years), and to assess their contribution to hospital admission; to explore the appropriateness of drug therapy according to the Beers' criteria.

Methods:

Cross-sectional observational survey of 110 elderly patients admitted during three non-consecutive months to the geriatric ward of a university hospital. Explorative assessment of appropriateness of drug therapy prior to hospital admission based on the Beers' criteria.

Results:

A DRP was the dominant reason for hospital admission in 14 out of the 110 patients (12.7%); for another 9 patients (8.2%), a DRP was partly contributing to hospital admission. For these 23 patients, adverse drug reactions and non-compliance were the most important types of DRPs. We found no relationship between drug related hospital admission and intake of a drug listed in the Beers criteria for inappropriate drug use in the elderly. Patients admitted for a DRP took more drugs before admission than patients admitted because of other reasons.

Conclusions:

DRPs are an important cause for admission on the geriatric ward of our hospital. The drugs causing DRPs in this study were not those listed in the Beers list of inappropriate drugs in the elderly.

Keywords:

Drug related problem (DRP), adverse drug reaction (ADR), drug therapy failure (DTF), hospital admission, drug use, elderly, Beers' criteria.

INTRODUCTION

Numerous studies show that elderly patients often experience drug related problems leading to hospital admission. The reported percentages vary however considerably, from 4 to 30% ^[1-13]. The majority of these problems concerns adverse drug reactions, and several studies have estimated that 50% to 97% of drug related problems in the elderly were avoidable ^[1,2,4-6,14].

The aim of this study was to investigate in depth the typology of drug related problems (DRPs) in geriatric patients (> 65 years) admitted to the acute geriatric ward of a university hospital, and to assess the contribution of these DRPs to hospital admission. In addition, we wanted to evaluate the appropriateness of drug therapy in these patients, using the Beers' criteria of inappropriate prescribing ^[15,16].

METHODS

Setting and study design

This study was performed on the geriatric ward of the Ghent University Hospital, Belgium (30 beds), after approval of the institutional Ethics Committee. More than 75% of the elderly persons admitted to our institution enter the hospital via the emergency department. If no surgery is planned, they are transferred in function of their medical condition to one of the wards for internal medicine; in case they do not present a specific condition, or if they are confused or suffer from dementia, they are transferred to the geriatric ward. Patients hospitalised at the geriatric ward are on average older than other hospitalised patients; other wards where older persons are cared for include neurology, cardiology and pneumology.

The patients admitted during 3 non-consecutive periods (October 2002, March 2003 and June 2003) were screened at admission for drug related problems. Drug use prior to and during admission was registered, and length of stay and mortality during hospitalization was recorded. A panel consisting of the treating geriatrician, a clinical pharmacologist and a hospital pharmacist reviewed the clinical chart and the drug list of all admitted patients.

Data collection

Drug use prior to admission was registered as usual. After initial registration in the emergency department, this is further completed at the geriatric ward, where both nurse and physician question the patient and/or his/her family. If there is no referral letter, or when there are doubts about the home medication, the general practitioner or the nursing home is contacted. Special attention is paid for drugs started less than one month before hospital admission, and for drugs in relation to the central nervous system (e.g. hypnotics). Drug use during the hospital admission was found in the nursing file, and was double checked with the pharmacy files for concordance. Drugs at discharge were registered by means of the discharge letter. All drugs taken prior to admission, during and after admission, were introduced in an Access database, based on a list of drugs available in Belgium.

Definition of drug related problems

The panel determined whether no, one or several DRPs were present in each patient, and classified each DRP, using the typology of Hallas^[17].

In this classification (see Table 1), a distinction is made between *adverse drug reactions* (ADRs) and *drug therapy failures* (DTFs). An *adverse drug reaction* is defined according to the WHO definition^[18] and further classified as occurring with normal use, overdose, contra-indication or drug interaction. A *drug therapy failure* is defined as a lack of therapeutic effect due either to drug non-compliance, a too low prescribed dose, or a drug-drug interaction. In this classification, untreated indication and drug use without (validated) indication are not taken into consideration.

To confirm the drug related nature of the problem, in a next step, the causality of the drug related problems is evaluated with a set of six criteria for ADRs, and a set of five criteria for DTFs (see Table 1). In a final step the potential contribution of a DRP to the hospital admission is assessed by classifying the DRP as a dominant, a partly contributing, a less important, or a not contributing factor to the hospital admission.

ADRs with unlikely or unevaluable causality and DTFs with a possible, unlikely or unevaluable causality were not taken into account for analysis. Furthermore, an admission was considered as related to an ADR or DTF when the symptoms were found to be the dominantly or partly

contributing reason for the hospital admission. All this was assessed by the panel, after discussion until consensus was reached.

Criteria for inappropriate drug therapy

The criteria developed by Beers and colleagues, updated in 1997, were used to assess inappropriate drug use ^[16]. These criteria list drugs that should generally be avoided in the elderly, doses or frequencies of administration that should not be exceeded, and drugs that should be avoided based on drug-disease interactions. We only used the list of drugs that should generally be avoided independent of diagnosis, and translated this to the drugs available on the Belgian market (*list available upon request*).

Data analysis

Patients were divided into two groups according to whether or not a drug related problem, dominantly or partly contributing, was present at admission. We then tested statistically for various variables the difference between the two study groups, in order to detect risk factors for drug related hospital admission.

The Mann-Whitney U-test was used for assessing differences in age, length of stay, total number of drugs and number of inappropriate drugs taken before admission as well as at discharge. We also evaluated whether gender, residence in a nursing home, previous admission during the last six months, or death during admission was related to a DRP that dominantly or partly contributed to hospital admission by using the Fisher's exact test. Furthermore, the overall difference between the number of drugs taken at home and the number of drugs taken at discharge was tested by the Wilcoxon signed-ranks test.

Statistical analysis was performed using the R Development Core Team software (version 2.6.1, 2007) ^[19].

RESULTS

During the three non-consecutive months of the study, 110 patients (41 men, 69 women) were admitted to the geriatric ward, directly, via the emergency department or after transfer from another hospital ward. Their mean age was 82.7 years and their mean length of stay at the geriatric ward was 16.6 days (1 – 50, median 14 days). Twenty percent of the patients (n=22) came from a nursing home, and thirty percent (n=33) had already been admitted to our hospital during the previous six months. Ten patients died during the hospital stay. The mean number of drugs per patient at admission was 5.9 (0 – 15, median 6) (Table 2). Overall, the number of drugs at discharge was significantly increased ($p < 0.001$), with a mean of 7.1 drugs per patient (0 – 15, median 7). At discharge, there was a decrease in the use of psychotropic drugs, and an increase in the use of laxatives.

a) Drug related problems

The panel (treating geriatrician, clinical pharmacologist and hospital pharmacist) identified the presence of a drug related problem with a definite, probable or possible causality at the time of admission in 35 patients (31.8%), namely 22 ADRs and 13 DTFs. For 31 of the 35 DRPs, there was a probable causal relationship between the drug and the symptoms, for 3 a definite relationship and for one DRP the causality was estimated as possible. For 14 of the 110 patients (12.7%), the DRP was considered to be the dominant reason for hospital admission; for another 9 patients (8.2%), the DRP was thought to partly contribute to hospital admission. Seven DRPs were found to be less contributing to hospital admission, and five DRPs were found not to contribute. We focused on the problems that contributed dominantly or partly to hospital admission (n=23).

b) Drug related hospital admissions

As shown in Table 3, the DRPs that were dominantly or partly contributing to hospital admission concerned 14 ADRs (8 normal use, 4 intentional overdose, one unintentional overdose and one drug interaction), and 9 DTFs (6 non-compliance and 3 subtherapeutic dose). The DRPs concerned central nervous system medication (9), antidiabetics (3), respiratory drugs (3), cardiovascular drugs (2), anti-inflammatory drugs (2), and four other classes. Nineteen drugs were

taken orally, 3 by inhalation (respiratory drugs) and 1 drug was administered subcutaneously (insulin).

Patients admitted dominantly or partly because of a drug related problem, took a significantly higher number of drugs before admission ($p=0.03$), and at discharge ($p=0.03$). Furthermore, patients who had been hospitalised during the previous six months, were more likely than the others to develop a DRP leading to hospital admission ($p=0.04$).

No relationship between drug related hospital admission and sex or coming from a nursing home, was found. The patients who were admitted because of a DRP were slightly younger (mean 80.3 years) than those admitted for other reasons (mean 83.9 years) ($p=0.04$). The patients admitted because of a DRP stayed longer in the hospital in comparison with the others; however, this difference (4,5 days in total length of stay) was not statistically significant. No relationship was found with death during hospital stay (see Table 4).

c) Inappropriate drug use according to Beers' criteria

Before hospital admission, 22 patients (20%) took a drug listed in the Beers' criteria of inappropriate drugs (9 different drugs); this concerned 5% of the overall drug use before admission. This number was reduced at discharge, to 18 patients (16%) taking an 'inappropriate' drug (8 different drugs), concerning 3% of the overall drug use at discharge. Two out of the 23 drugs that caused dominantly or partly hospital admission were 'inappropriate', namely lorazepam (> 2.5 3 mg) and diazepam. No relationship was found between the intake of an 'inappropriate' drug listed by Beers, and the occurrence of a DRP leading dominantly or partly to hospital admission ($p>0.05$).

DISCUSSION

Incidence and types of drug related hospital admissions

We found that drug related problems at the time of hospital admission were common, and one out of five patients was suffering from a drug related problem that required hospitalization or

contributed to it. When comparing studies about this subject, we have to consider the definition of drug related problems, and the definition of drug related hospital admissions used in these studies. The definition of drug related problems varies from study to study. In all the publications in the reference list below, adverse drug reactions were considered, although not all studies included the ADRs originating from intentional overdose. In some studies also inappropriate drug choice, untreated indications and drug use without indication were taken into account. In our study, we did not include these aspects, since it was our goal to focus on problems that could be clearly linked to the use of drugs, and since information about previous medical decisions would probably not often be available.

Applying the method established by Hallas et al. ^[17], we found an incidence of 20.9% of drug related hospital admissions. When we limit to ADR related hospital admissions, we found an incidence of 12.7% and when excluding intentional overdoses, the incidence was 9.1%. In other studies, similar incidences of ADR related hospital admissions were found. Beijer et al. ^[1] published a meta-analysis in 2002, in which 17 studies about ADR related hospitalizations in the elderly were included, and found a mean incidence of 16.6%. The authors of this meta-analysis remarked that the studies included were relatively small sized, varying from 100 to 1988 hospitalizations, and that large studies (>2000 patients) were lacking. Later, larger studies about drug related hospitalizations of the elderly were performed in Great Britain ^[11] (18000 patients), Italy ^[12] (12000 patients), and in the Netherlands ^[13] (> 660000 patients). The incidence of ADR related hospital admissions (dominant reason for hospital admission) was estimated at respectively 5.2% ^[11], 3.4% ^[12], and 3.2% ^[13]. Only a few publications also included other types of drug related problems, such as non-compliance, subtherapeutic dose, and inadequate monitoring. A study performed in the UK in 1997 with about 1.000 elderly patients found an incidence of 5.3% overall drug related hospital admissions ^[5]. Another study in the UK in 2001 with more than 4.000 patients of all ages, found 6.5% of admissions to be drug related ^[7]. As discussed in the paper of Beijer et al. ^[1], it seems that larger studies seem to find lower incidences of drug related admissions. This might be due to a less intensive or retrospective screening system, while smaller sized studies allow a more accurate recording of drugs and symptoms based on medical, nursing and laboratory findings, and a multidisciplinary assessment of causality and contribution to hospital admission. Another factor

which could explain the relatively high incidence of drug related hospital admissions we found is the fact that our study was performed at a geriatric ward, where concern about medication use is high, and registration and evaluation of drugs used before admission is performed extensively. Furthermore, the patients we studied took a high number of drugs, which is a well known risk factor for developing adverse drug reactions ^[20-23], as confirmed in our study. Our finding that the number of drugs at discharge was higher in the patients hospitalised dominantly or partly because of a drug related problem, requires careful evaluation, since hospitalization is most often a milestone in worsening clinical condition, including step-ups in pharmacotherapy. In our patients, drug related hospital admissions were also more frequent in somewhat younger patients. Although statistically significant, we have no clinically relevant interpretation for it.

Criteria for inappropriate use

Only a small percentage of the drugs used before admission and at discharge were inappropriate according to the Beers' criteria. We found no relationship between intake of 'inappropriate' drugs, and the occurrence of a DRP leading dominantly or partly to hospital admission. Beers' criteria have been criticized, since they do not identify all causes of potentially inappropriate prescribing ^[24]. Indeed the process of selecting a drug in relation to indication and contra-indications, choice of dosage and duration of therapy, and the monitoring for adverse drug reactions or interactions, is more important than the drug itself. It has therefore been argued that although the Beers' criteria have been widely used and represent a standardized tool for pharmacological research, they cannot be considered as a substitute for careful clinical judgement ^[25].

Strengths and weaknesses

The strength of this study is that drugs used before, during and after admission, were recorded accurately, and the assessment of the contribution of drug related problems to hospital admission was performed through a process of multidisciplinary consensus reaching between the panel members. Therefore, we chose for a small but in-depth study. Secondly, we tried to define relevant drug related problems in such a way that they could be clearly linked to the use of drugs. This led us further into understanding the nature of drug related problems in the elderly, i.e. the

sensitivity of frail elderly people to well-known adverse drug reactions and the risk of non-compliance with deterioration of diseases as a consequence. This means that drug use in the elderly is a difficult equilibrium, with small changes in response resulting in adverse drug reactions or worsening of the clinical condition; therefore, follow-up and monitoring is extremely important to reach or maintain this equilibrium.

We are aware that our study has several limitations. A formal screening method for identification of drug related problems such as the Medication Appropriateness Index (MAI) was not used ^[26,27], nor a method for inter-rater variability scoring. Furthermore, the number of patients included was relatively small.

Prevention strategies

Inappropriate prescribing for frail elderly persons as well as inadequate communication between primary and hospital care have been mentioned in the literature as causes of drug related problems ^[14,24,27-32]. Appropriate prescribing is not only about drug choice, but includes also careful evaluation of doses, duration of therapy, monitoring for adverse reactions and drug-drug interactions. As elderly people are often treated by several physicians, there is a risk for polypharmacy and therefore the occurrence of drug related problems. A number of actions can be taken in hospitals, to stimulate appropriate prescribing and to assure adequate communication between primary and hospital care:

- education of caregivers;
- accurate recording of drugs used;
- multidisciplinary medication review with advice of clinical pharmacists and clinical pharmacologists;
- informing patients about changes in drug regimens and about newly started drugs;
- informing first-line caregivers (general practitioners, care workers) about changes in drug regimens and advice for follow-up;
- electronic patient files and computer assisted prescribing.

For these actions, attention should focus mainly to patients taking a high number of drugs.

CONCLUSION

This study confirms that drug related problems represent an important problem in geriatric patients admitted to the hospital, and that there is a significant contribution of these problems to hospitalization (20.9%). We found a positive correlation of these problems with the number of drugs used, but not with treatment with inappropriate medications defined by Beers. Although the study size and the methodology used can be criticised, we consider this study to be useful because the analysis was ~~thoroughly~~ performed thoroughly. In order to prevent drug related problems in the elderly, we recommend to focus on multidisciplinary medication review for elderly patients admitted in hospitals, and to pay attention to all aspects of pharmacotherapy, e.g. side effects, under- or overdose, drug-drug interactions, duration of therapy and non compliance.

ACKNOWLEDGEMENTS

The authors are indebted to the participating geriatricians prof. dr. M. Afschrift, prof. dr. N. Van den Noortgate, dr. H. Martens, dr. N. Van Doninck, and dr. A. Velghe, to Head Nurse H. Van Doninck, and the patients of the geriatric ward. This study was not funded and the authors have no conflicts of interest.

TABLES

Table 1: Assessment of drug related problems according to Hallas [6]

Typology of drug-related problems

Adverse drug reactions (ADRs)

- Occurring during normal use
- caused by overdose
- caused by non-respect of a contra-indication
- caused by drug interaction

Drug therapy failures (DTFs)

- caused by drug non-compliance
- caused by underdosing
- caused by a drug-drug interaction

Criteria for assessment of causality of ADRs

1. a known ADR or toxic reaction;
2. a reasonable temporal relationship between beginning drug therapy and onset of ADR;
3. disappearance of the ADR on discontinuation or dosage reduction;
4. inability to explain the symptom or event by other conditions or predisposition of the patient;
5. reappearance of the symptoms on re-exposure, or laboratory tests showing toxic drug levels or drug-induced metabolic disturbances that explain the symptom;

The causality of the relationship is accepted as

- 'definite' when all 5 criteria are satisfied,
- 'probable' when 1 through 4 are satisfied,
- 'possible' when 1 through 3 are satisfied,
- 'unlikely' or 'unevaluable' when the necessary information cannot be obtained or other conditions are considered to be more likely the cause of the symptoms.

Criteria for the assessment of causality of Drug Therapy Failures

1. the symptoms of the disease are known to reappear at insufficient doses;
2. the symptoms are not likely to have been caused by progression of the disease;
3. a reasonable temporal relationship between the start of inadequate dosage and the appearance of symptoms;
4. resolution of the symptoms upon adjustment to an adequate dose;
5. no other conditions that explain the symptoms;
6. drug levels clearly below the therapeutic range or clear evidence of intake of an insufficient dose.

The causality of the relationship is accepted as

- 'definite' when all criteria are satisfied,
- 'probable' when 1 through 5 are satisfied,
- 'possible' when 1 through 4 are satisfied,
- and 'unlikely' or 'unevaluable' when the necessary information cannot be obtained or other conditions are considered to be more likely the cause of the symptoms.

Contribution of ADR or DTF to hospital admission

- 'dominant': drug-related symptoms are the main reason for admission and no other symptoms contribute significantly
- 'partly contributing': drug-related symptoms are a substantial reason for admission, but other factors are also present
- 'less important': drug-related symptoms play a minor or uncertain role, and the patient would most likely have been admitted without them
- 'not contributing': symptoms other than the drug-related symptoms are the main reason for admission

Table 2: Demographic data of the patients admitted during the study period (n=110)

	Mean	Median	Range	SD
Age (years)	83.2	82.7	65.5 – 102.5	7.5
Total length of stay (days)	19.6	16	1 – 85	14.3
Length of stay at the geriatric ward (days)	16.6	14	1 – 56	10.9
Number of drugs taken before admission (n=100)	5.9	6	0 – 15	3.1
Number of drugs taken at discharge (n=100)	7.1	7	0 – 15	3

Table 3: Drug related problems that contributed dominantly or partly to hospital admission (n=23)

Type of DRP	Drug	Symptoms	Causality	Contribution to admission
ADR drug interaction (1)	risperidone, citalopram, mirtazapine	muscle weakness, dehydration, disorientation	probable	partly contributing
ADR normal use (7)	amiodarone diclofenac metformin, insulin methylprednisolone naproxen salbutamol thalidomide	toxic hepatitis stomach irritation, abdominal pain symptomatic hypoglycaemia haemoptysis gastric haemorrhage supraventricular tachycardia somnolence	probable probable probable probable probable probable	dominant partly contributing dominant partly contributing dominant partly contributing partly contributing
ADR unintentional overdose (2)	lorazepam metformin	fall symptomatic hypoglycaemia	probable probable	dominant dominant
ADR intentional overdose (4)	acetylsalicylic acid diazepam opioids tilidine/naloxon	poisoning (established) somnolence, confusion, falls somnolence, intoxication somnolence, ataxia, nausea	probable probable probable probable	dominant partly contributing dominant partly contributing
DTF non-compliance (6)	amoxyclav anti-asthmatics antidepressive agents formoterol + corticoid levothyroxine neuroleptics	dyspnoea, coughing, sputa COPD exacerbation, dyspnoea depressive, walking around at night dyspnoea, coughing dyspnoea, stridor confused, aggressive	definite probable probable definite probable definite	dominant dominant dominant dominant dominant dominant
DTF subtherapeutic dose (3)	anti-epileptics insulin sotalol	seizure with absence and urine loss symptomatic hyperglycaemia atrial fibrillation	probable probable probable	partly contributing dominant partly contributing

ADR = adverse drug reaction

DTF = drug therapy failure

Table 4: Drug related hospital admissions (DRHA) in relation to demographic data and other variables

	Mean	DRHA (n=23)	Non-DRHA (n=87)	p-value
Age (years)	83.2	80.3	83.9	0.0436
Total length of stay (days)	19.6	23,2	18.7	0.248
Length of stay at the geriatric ward (days)	16.6	19.4	15.9	0.395
Number of drugs taken before admission	5.9	6.9	5.7	0.0285
Number of drugs taken at discharge	7.1	8.3	6.8	0.0313
	Number of patients	DRHA (n=23)	Non-DRHA (n=87)	p-value
Readmission	33	11	22	0.0437
Death during hospital stay	10	0	10	0.117
Coming from a nursing home	22	4	18	1.0
'Inappropriate' drug (Beers list) at admission	22	6	16	0.534

REFERENCES

1. Beijer HJM, de Blaey CJ. Hospitalizations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharmacy World & Science* 2002; 24: 46-54
2. Chan M, Nicklason F, Vial JH. Adverse drug events as a cause of hospital admission in the elderly. *Internal Medicine Journal* 2001; 31: 199-205
3. Mannesse CK, Derkx FHM, de Ridder MAJ, et al. Contribution of adverse drug reactions to hospital admission of older patients. *Age and Ageing* 2000; 29: 35-39
4. Courtman B, Stallings S. Characterization of drug-related problems in elderly patients on admission to a medical ward. *Can J Hosp Pharm* 1995; 48: 161-166
5. Cunningham G, Dodd TRP, Grant DJ, et al. Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment. *Age and Ageing* 1997; 26: 375-382
6. Hallas J, Harvald B, Worm J, et al. Drug-Related Hospital Admissions - Results from An Intervention Program. *European Journal of Clinical Pharmacology* 1993; 45: 199-203
7. Howard RL, Avery AJ, Howard PD, et al. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: observational study. *Qual Saf Health Care* 2003; 12: 280-285
8. Kaiser RM, Schmader KE, Pieper CF, et al. Therapeutic failure-related hospitalizations in the frail elderly. *Drugs Aging* 2006; 23: 579-586
9. Nelson KM, Talbert RL. Drug-related hospital admissions. *Pharmacotherapy* 1996; 16: 701-707
10. Hohl CM, Dankoff J, Colacone A, et al. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. *Annals of Emergency Medicine* 2001; 38: 666-671
11. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; 329: 15-19
12. 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: 1962-1968
13. van der Hooft CS, Sturkenboom MC, van Grootheest K, et al. Adverse drug reaction-related hospitalizations: a nationwide study in The Netherlands. *Drug Saf* 2006; 29: 161-168
14. Lindley CM, Tully MP, Paramsothy V, et al. Inappropriate Medication Is A Major Cause of Adverse Drug-Reactions in Elderly Patients. *Age and Ageing* 1992; 21: 294-300
15. Beers MH, Ouslander JG, Rollinger I, et al. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med* 1991; 151: 1825-1832
16. Beers MH. Explicit criteria for determining inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; 157: 1531-1536
17. Hallas J, Harvald B, Gram LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med* 1990; 228: 83-90

18. International monitoring of adverse reactions to drugs. Adverse reaction terminology. Uppsala: WHO Collaborating Centre for International Drug Monitoring. 2008;
19. R Development Core Team (2007). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, <http://www.R-project.org>. 2008;
20. van den Bemt PM, Egberts AC, Lenderink AW, et al. Risk factors for the development of adverse drug events in hospitalized patients. *Pharm World Sci* 2000; 22: 62-66
21. Field TS, Gurwitz JH, Avorn J, et al. Risk factors for adverse drug events among nursing home residents. *Arch Intern Med* 2001; 161: 1629-1634
22. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc* 2004; 52: 1349-1354
23. Hajjar ER, Hanlon JT, Artz MB, et al. Adverse drug reaction risk factors in older outpatients. *Am J Geriatr Pharmacother* 2003; 1: 82-89
24. Gurwitz JH, Rochon P. Improving the quality of medication use in elderly patients: a not-so-simple prescription. *Arch Intern Med* 2002; 162: 1670-1672
25. Onder G, Landi F, Cesari M, et al. Inappropriate medication use among hospitalized older adults in Italy: results from the Italian Group of Pharmacoepidemiology in the Elderly. *Eur J Clin Pharmacol* 2003; 59: 157-162
26. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992; 45: 1045-1051
27. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet* 2007; 370: 173-184
28. Hanlon JT, Pieper CF, Hajjar ER, et al. Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay. *J Gerontol A Biol Sci Med Sci* 2006; 61: 511-515
29. Ong SW, Fernandes OA, Cesta A, et al. Drug-related problems on hospital admission: relationship to medication information transfer. *Ann Pharmacother* 2006; 40: 408-413
30. Passarelli MC, Jacob-Filho W, Figueras A. Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. *Drugs Aging* 2005; 22: 767-777
31. Coleman EA, Smith JD, Raha D, et al. Posthospital medication discrepancies: prevalence and contributing factors. *Arch Intern Med* 2005; 165: 1842-1847
32. Royal S, Smeaton L, Avery AJ, et al. Interventions in primary care to reduce medication related adverse events and hospital admissions: systematic review and meta-analysis. *Qual Saf Health Care* 2006; 15: 23-31

APPENDICES

Appendix 1: Drugs listed by Beers existing in Belgium (status: 2002)

Based upon: Beers MH. Explicit criteria for determining inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; 157: 1531-1536

Generic name
Propoxyphene
Indometacine
Phenylbutazone
Pentazocine
Oxybutynin
Flurazepam
Amitriptyline
Perphenazine-amitriptyline
Doxepine
Meprobamate
Lorazepam > 3mg
Oxazepam > 60 mg
Alprazolam > 2 mg
Temazepam > 15 mg
Triazolam > 0,25 mg
Diazepam
Disopyramide L.A.
Digoxine > 0,125 mg
Dipyridamole
Methyldopa
Chlorpropamide
Belladonna alkaloids
Chlorpheniramine
Diphenhydramine
Hydroxyzine
Cyproheptadine
Promethazine
Dexchlorpheniramine
Ergot mesyloids
Ferrous sulfate > 325 mg
Ticlopidine

Chapter 3: The use of hypnosedative drugs in a university hospital: has anything changed in ten years time?

This chapter is based upon:

Somers A, Robays H, Audenaert K, Van Maele G, Bogaert M, Petrovic M. The use of hypnosedative drugs in a university hospital: has anything changed in ten years time? Eur J Clin Pharmacol 2011;67:723-9.

ABSTRACT

Aim:

To investigate the use of hypnotosedatives (HSs) before and during hospitalization; to explore the relationship between their use and various demographic and clinical variables; to compare the results with data from a similar study performed in 2000 with particular interest for the adherence to the hospital formulary guidelines.

Methods:

Cross-sectional observational survey of 326 hospitalised patients recruited from 10 wards of the Ghent University Hospital, with a patient interview and by evaluation of the medical and nursing files.

Results:

In 30.7% of the patients the use of a hypnotosedative (HS) before admission was reported. According to the patient interview, 33.1% of the patients used a HS during hospitalization. But, according to the medical and nursing files, the use of HSs in the hospital was 10% higher (43.3%). In 19.4% of the patients who took HSs before admission, their use was discontinued in the hospital. In 15.6% of the patients who took no HS before admission, a HS was started in the hospital, according to the formulary guidelines (data from files). There was a positive correlation between use of HSs in the hospital and older age, longer hospitalization, not coming from home, a higher number of HSs taken before hospitalization, sleeping problems emerging during hospitalization and CNS disorders respectively. In comparison with the year 2000, we registered a slight decrease in the use of HSs during hospitalization and a decrease in the number of newly started patients.

Conclusions:

The prevalence of HS use in our university hospital is high, mostly as a result of continuation of HSs that were started before admission, as there seems to be no general policy of active cessation. Compared to the survey performed ten years ago, fewer patients are newly started on HSs, and when this is the case, the formulary guidelines are followed.

INTRODUCTION

Hypnotosedatives (HSs) are widely prescribed for treatment of insomnia and anxiety, but their long-term use is a reason for concern, because of dependency, side effects, and cost ^[1-3]. Older patients are especially at risk for impaired cognitive and movement function, with an increased risk of inappropriate sedation, falls and fractures ^[4-6].

It is well known that the worldwide use of HSs is high, both inside and outside the hospital ^[7-10]. In Belgium, there is a high prevalence of HSs prescription: surveys conducted in 2001, 2004 and 2008 ^[11] demonstrated an increasing use of HSs (reported use during the last 2 weeks was 5%, 8% and 9% respectively), and found that the use of HSs increases with age (2004: 17% in patients aged 75 years or more). The Belgian Centre for Pharmacotherapeutic Information in its formulary gives guidance for treatment of acute and chronic insomnia, and advises short term use of benzodiazepines in case non-pharmacological approach is not helpful. However, the choice and dose of benzodiazepines that could be used are not mentioned, and no distinction is made between alprazolam or lorazepam and other benzodiazepines.

In 2000, we registered the use of HSs before and during hospitalization for 493 patients admitted to ten wards of our hospital. HSs were defined as benzodiazepines and benzodiazepine-like hypnotics (the so called Z-drugs, i.e. zolpidem, zaleplon and zopiclone); we also included two tricyclic antidepressants, i.e. mianserine (ATC N06AX03) and trazodone (ATC N06AX05), as in our hospital, these are only used for HS purposes, as well as the antihistaminic dimetindene (ATC R06AB03). We found that 29% of these patients took a HS at home and that in 14% of these patients the HS was discontinued during their hospital stay. Furthermore, a HS was prescribed in the hospital in 45.2% of the patients in total and in 28.6% of the 493 patients a HS was started ^[12].

In view of this high consumption, the hospital formulary guidelines (available upon request) were adapted and distributed throughout the hospital. Briefly, in case of sleeping problems, HSs are not recommended; in case of persisting and debilitating inner tension or adjustment problems, an intermediate-acting hypnotosedative is recommended (e.g. lormetazepam or lorazepam), in a low dose and for a short period of time (preferably only once, maximum 1 or 2 weeks). These guidelines were published in the hospital formulary in 2003 and in 2005 as a printed version, which was sent to the medical staff and all head nurses. In 2007, an electronic drug bulletin was

distributed with precise recommendations in case a HS is necessary, namely to prescribe lormetazepam 1 mg for a short period of time, and to stop newly started treatment before discharge. It was also stipulated in the drug bulletin that gradually discontinuation of HSs started before hospitalization should be considered.

We repeated the registration in 2009, to evaluate whether the prevalence and dynamics of HS use was changed. Moreover, we wanted to collect more clinical data, in order to search for risk factors for HSs use which could orient us to more targeted actions.

METHODS

Setting and study design

This prospective, observational, monocentric study was initiated by the Pharmacy and Therapeutic Committee of the Ghent University Hospital, Belgium and performed on ten hospital wards after approval of the hospital Ethics Committee. The same definition of HSs was used as in the previous study. The ten wards were those where the registration in the year 2000 was performed. The wards included were cardiology, pneumology, nephrology, psychiatry, physical rehabilitation, maternity, head and neck surgery, thoracic and vascular surgery, plastic surgery and abdominal surgery. Five of these wards had the highest and five wards had the lowest consumption of HSs in the year 2000. The method was identical, namely patient interview (after informed consent) by means of a questionnaire, and examination of the medical and nursing files. The interview used in 2009 was almost identical with the one used in 2000. The examination of the medical and nursing files was somewhat altered due to the implementation of electronic prescribing on half of the ten wards. The patients' health problems were also recorded.

We included only patients who stayed at least two nights in the hospital, and interviewed all consecutively admitted patients to the ten hospital wards, during a six weeks period per ward.

Data collection

The use of HSs before and during hospitalization was measured by means of a patient interview and by examination of the nursing and medical files. The interview took place on a random day during the patient's hospital stay, mostly about a week after admission but this was different

depending on the length of stay. Before the interview, the patient was informed about the purpose of the study and was asked for written informed consent.

The patient interview (available upon request) consisted of 18 questions concerning sleeping problems and HS use before and during hospital stay, and additionally questioned the intended HS use after discharge. The information on HS use was completed with information from the medical and nursing files, done at the moment of patient interview and at the moment of the discharge. In addition, the reason for hospitalization and the health problems, based on a predefined list of 36 items, were registered. These 36 items were grouped into 9 categories namely cardiovascular, respiratory, gastro-intestinal, metabolic disorders, blood related disorders, infection, malignancy, central nervous system pathology, and orthopaedic and gait disorders. Metabolic disorders mainly concerned diabetes and furthermore acute and chronic renal insufficiency, gout and osteoporosis; central nervous system pathology included amongst others dementia, depression, epilepsy, Parkinson's disease and peripheral neuropathy.

Demographic data that were collected concerned age, gender, origin (home, nursing home, other hospital), and length of stay. The data collection was performed by a hospital pharmacist.

Data analysis

The data were processed in Microsoft Access and transposed to SPSS version 17 for statistical analysis. The influence of age, residence before hospitalization and previous HS use on sleeping problems and on the number of used HSs before and during hospitalization was assessed by a Chi-Square Test (Fisher's exact test and linear-by linear association) and by logistic regression. The difference in HS use before, during, and after hospitalization was analysed by the Friedman test and by the Wilcoxon signed-ranks test. The McNemar test was used for determining the difference between sleeping problems before and during hospitalization. The influence of age and length of stay on sleeping problems was assessed by the Mann-Whitney U-test. The Spearman coefficient was used to analyse the correlation between age and length of stay on the one hand and use of HSs on the other hand. Finally, the difference between HS use in the year 2000 and the year 2009 was assessed by a Chi-square test.

RESULTS

Demographics and health problems

During the 2.5 months of the survey, 330 patients were asked to participate; four of them did not accept. The demographic data of the 326 included patients are shown in Table 1. This population consisted of 155 females (47.5%) and 171 males (52.5%). Their mean age was 53.5 years (SD 18.6 years). Twelve patients were transferred from a nursing home, 27 from another hospital, and 287 were living at home before admission. The mean length of hospital stay was 19.1 days (SD 31.8 days, median 9 days). Four of the patients died during their hospital stay.

The distribution of the patients over the ten wards as well as the length of stay per ward is presented in Table 2. During the 6 week survey, around 40 patients were included per ward, except for the rehabilitation and the psychiatry ward, because of longer length of stay and less turn-over of patients as a consequence. In addition, the study duration was shorter for the abdominal surgery ward because of a delay in agreement for participation in the study.

Most of the patients included in the study suffered from cardiovascular disorders (31.0%), followed by metabolic disorders (28.5%), malignancy (15.0%), respiratory disorders (14.1%), gastrointestinal disorders (9.5%), central nervous system disorders (9.2.%), orthopaedic or gait disorders (7.7%), infection (4.9%), or blood related disorders (2.8%).

Sleeping problems and hypnotic use before admission

The patient interview revealed that 131 of the patients (40.2%) suffered from sleeping problems before hospitalization; out of these 131 patients, 80 (61.1%) took a HS on a regular basis. Out of the 195 patients who did not report sleeping problems before admission, 20 (10.3%) did use a HS, resulting in a total of 100 (30.7%) patients using HSs before admission (Table 3).

The main reasons for HS use mentioned by the patients were a sleep initiation problem (n=68) or a sleep maintenance problem (n=36), as well as nervousness (n=30), fear (n=7) and pain (n=4). Seventeen percent of the patients that took HSs before admission had been given information on future discontinuation of HS use by the treating physician.

According to the medical and nursing files, HS were used before admission by 108 patients, with a total of 153 HSs. Thirty-three patients used more than 1 HS before admission (22 patients took 2

HSs, 10 patients took 3 HSs and 1 patient took 4 HSs). The most frequently used HSs were alprazolam (21.3%), lorazepam (18.7%), zolpidem (14.8%) and lorazepam (11.0%).

A Fisher's exact test revealed that females reported more sleeping problems before hospitalization than males (females 47.1% versus males 33.9%, $p = 0.017$). Suffering from a metabolic disorder was positively correlated with sleeping problems before hospitalization (metabolic disorder 52.7% versus no metabolic disorder 32.2%, $p = 0.002$). A Mann-Whitney test showed that patients dealing with sleeping problems before admission were significantly older ($p = 0.001$).

Sleeping problems and hypnotic use during hospitalization

Concerning sleeping problems in the hospital, 84 patients mentioned a combination of sleep initiation and sleep maintenance troubles (25.8%), 57 patients mentioned sleep maintenance problems (17.5%) and 38 patients mentioned sleep initiation problems (11.7%). In total, 179 patients (or 54.9 % of the study population) had difficulties to sleep in the hospital.

According to the patient interview, 80 patients with sleeping problems, and 28 patients without sleeping problems, took a HS during hospitalization, resulting in a total of 108 patients or 33.1% of the total study population (Table 3). Ninety of these 108 patients were aware of the brand name.

The main reasons for HS use in the hospital mentioned by the patients, were continuation of HS use before admission ($n=51$), sleeping problems emerging in the hospital ($n=36$), worsening of already existing sleeping problems in the hospital ($n=7$), fear ($n=19$) and pain ($n=6$). According to the patient interview, 35 patients were newly started on HSs during hospitalization (i.e. 15.5% of the patients who did not take a HS before admission). Information about discontinuation of HSs in the future was given by the treating physician to 2 patients that were newly started on HSs during hospitalization (5.7%).

According to the medical and nursing files, HS use during hospitalization was found for 141 patients (43.3%), with a total of 235 HSs, although not all HSs were used at the same time (Table 3). For 66 of the 141 patients who took a HS, more than one HS was prescribed (46.8%): 45 patients took 2 HSs, 14 took 3 HSs and for 7 patients 4 HSs were prescribed. Use of more than one HS was more frequent on the psychiatry, thoracic and vascular surgery, rehabilitation, plastic surgery and abdominal surgery wards. For 49 HSs in total, it was not clear whether the drug was

effectively administered, and for 18 patients, the use was only upon request. Only for 83 HSs, a starting and stopping date was found.

According to the patient files, ~~HSs were newly started in~~ a higher percentage of patients were newly started in HSs in comparison to what was reported in the patient interviews, namely 49 (22.5%), but after exclusion of upon request orders without real HS use and after exclusion of a single administration (e.g. before endoscopic procedures), we found that HSs were newly started in 34 patients were newly started on HSs during hospitalization (15.6%). Most of these patients were admitted at a surgical ward (53.3%), or at the rehabilitation ward (26.7%).

The most frequently HSs prescribed during hospitalization were lorazepam (32.3%), alprazolam (23.4%), and lorazepam (15.3%). For 18 patients (12.8%), the HS was prescribed upon request and for 83 HSs (35.3%) a starting and stopping date was found.

The linear-by-linear association showed a strong correlation between sleeping problems at home, and the number of used HSs before, during, and after hospitalization. Sleeping problems emerging in the hospital were correlated with the number of HSs used in the hospital ($p = 0.002$), but not with the number of HSs used before admission ($p = 0.053$). The Spearman correlation test revealed a positive correlation between HS use (before, during and after hospitalization) and older age ($p < 0.001$), and between HS use during hospitalization and length of stay ($p < 0.001$). Furthermore, the linear-by-linear association showed a positive correlation between use of HSs in the hospital and not coming from home ($p = 0.032$), a higher number of HSs taken before hospitalization ($p < 0.001$) and CNS disorders ($p < 0.001$).

The highest prevalence of HS use was found on the rehabilitation, psychiatry, plastic surgery, thoracic and vascular surgery and cardiology wards. When the patients of the maternity ward are excluded (since there was no use of HSs found), we come to a prevalence of nearly 50% of the patients taking a HS during hospitalization.

Hypnosedative use after discharge

The patient interviews learned that for 27 patients from the 100 patients who declared to take a HS at home, the HS was stopped during hospitalization (27.0%). Two of these patients told they wanted to restart the HS, one patient hesitated. For the 73 patients who continued to take the HS

in the hospital, 57 patients (76%) told they wanted to continue after discharge, 8 patients (11%) said they wanted to stop, and 8 patients (11%) had not yet decided.

According to the discharge documents, for 21 of the 108 patients who took a HS before admission, the use of HSs was to be discontinued (19.4%), and for 58 patients (17.8%), use of a HS after discharge was envisaged (Table 3). Out of the 21 patients in whom the HS use was stopped, 9 were admitted at a surgical ward and 12 at an internal medicine ward. A linear-by-linear association showed no correlation between sleeping problems in the hospital and intended use of HSs after discharge ($p = 0.73$).

Comparison between 2000 and 2009

The mean and median age of the patients of 2009 was almost the same as in 2000 (mean age: 53.5 years in 2009 and 53.7 in 2000, median age was the same namely 55 years).

The percentage of patients using HSs before hospitalization was 29.0% in the year 2000 and 33.1% in 2009, but this difference was non-significant (Chi-square $p = 0.21$). There was a significant decrease in newly started patients (28.6% in 2000 versus 15.6% in 2009; $p < 0.001$), and a borderline significant increase in discontinued patients (14.0% in 2000 versus 19.4% in 2009; $p = 0.055$). Nevertheless, there was no significant decrease in percentage of patients using HSs during hospitalization (45.2% in 2000 versus 43.3% in 2009; $p = 0.58$), probably due to the higher percentage of patients using HSs before admission, that continued these drugs in the hospital.

DISCUSSION

Strengths and weaknesses

The strength of this study is that the use of HSs before and during, and the intended use after hospitalization, were recorded accurately, using different sources namely a combination of patient interview, and evaluation of the medical and nursing files. This gave us the opportunity to report highly reliable data about HS use. Furthermore, we searched for risk factors (medical and demographic data), to identify the patients that had the greatest risk of prolonged HS use.

Another strength is the possibility of comparison with the study performed in the year 2000, by using the same patient interview and by including the same hospital wards, which allowed us to evaluate the evolution of HS use.

Our study has several limitations. First of all, the formulary guideline was introduced only passively (by mail and by publication in the formulary), and was perhaps not enough known by the prescribing physicians. It could have been more effective if it would have been implemented in a more proactive way, e.g. by teaching or by prospective advice. Secondly, the wards were selected according to the HS use in the year 2000, namely five wards with the highest and five wards with the lowest consumption. This means that some wards were excluded, either with routine active cessation or with inappropriate HS therapy (e.g. the geriatric and pneumology ward), which could have biased our results. Therefore, in the future, a hospital wide survey would be more suitable, e.g. when electronic prescribing has been introduced in all hospital wards. Another limitation concerns the data at discharge, since use of HSs after discharge was extracted from the discharge documents, and follow-up of the patient (e.g. by telephone call) was not performed.

Use of HSs before and during hospitalization

We found a discrepancy between the patient interviews and the medical and nursing files. The lower incidence of HS use reported by the patients could be due to fact that use of a HS as an anxiolytic was not perceived as sleep medication; furthermore some patients, e.g. the severely ill, could not remember properly their medication use, and some HSs were started between the patient interview and the consultation of the patient files. One would expect however that the nursing file would list every administration of drugs during hospitalization correctly and would therefore be considered as the golden standard considering drug use. However, we noticed that in the nursing and medical files the drugs taken before admission were not always listed correctly (e.g. 'home medications to be continued') and sometimes home medications were kept by the patients themselves (although this is against the agreed procedures). This resulted in loss of information about stopping dates in the patient files, which made correct interpretation of combined HS use very difficult. For instance only for three of the seven patients for whom four HSs were prescribed, we can be sure that the four HSs were combined at the same time. It is therefore likely

that the real use of HSs was somewhere in between 33.1% (reported by the patients) and 43.3% (out of the medical and nursing files).

Notwithstanding the difference between patient interview and file registration, the prevalence of HS use before and during hospitalization to our hospital is high. In some published studies performed in hospitals, a large variability in HS use, from 15.7% to 45%, was reported ^[7,8,13-17]. The variability of the results could be due to the characteristics of the population studied, the method for data collection and the duration of the studies. Furthermore, some of these studies were not performed recently, and HS use has probably changed over time.

The comparison of the results from almost ten years ago to those now in the same hospital is probably more meaningful, and learns us that HS use during hospitalization has not decreased, mostly as a result of continuation of HSs started before admission, as there seems to be no general policy of active cessation. The positive news is that in comparison to ten years ago, a smaller number of patients were newly started on HSs in the hospital, and when this was the case, the formulary guidelines were followed.

Risk factors

We explored the risk factors for HS use during hospitalization. Since we found that information about discontinuation was provided for only 2 patients who were newly started, we can presume that the risk factors are predictive for prolonged use after discharge.

- Concerning demographic characteristics, HS use in the hospital was significantly higher in older patients, in patients who were not coming from home, and in patients who stayed longer in the hospital. The influence of age, length of stay and co-morbidities has also been found in previous studies ^[9,10,15,16].
- As for diagnosis, there was a positive correlation between use of HSs in the hospital and CNS disorders, as well as the intake of a HS before admission.
- With regard to doctors' characteristics, the HS use before admission could not be studied, but we explored more in detail the changes during hospitalization, and found that relatively more HSs were newly started, and fewer were actively stopped in patients at surgical wards, in comparison with internal medicine wards. However, this should be interpreted with caution

since this was a monocentric study in which not all hospital wards were included.

Actions for the future

Our results indicate that older patients who took HSs before admission and who suffer from co-morbidities (especially psychological disorders) are at risk of prolonged HS use. Since prolonged HS use especially in older patients can lead to side effects such as impaired cognitive and movement function, future preventive actions must take this population into consideration. We found that 143 of the 162 HS users (88.3%) were not informed by the treating physician about risk of dependence and were not stimulated to reduce HS use. The distribution of formulary guidelines for HS use has been useful for reducing initiation of HSs in the hospital, but another approach is needed for reduction of the high HS use, over the boundaries of the hospital setting.

As mentioned before, there is no general policy of active cessation of HS use in our hospital, and this is probably the same in many other hospitals. The finding that HSs are not often discontinued in the hospital can perhaps be explained by the fact that hospitalization in itself leads to anxiety and insomnia. Moreover, abrupt discontinuation is not recommended since this could lead to withdrawal symptoms. Hospitalization could however be the good moment for drug therapy optimization, especially for older patients with several co-morbidities ^[18]. Combined HS use should be discouraged to prevent adverse drug events, and clinicians should focus on short-term use in newly started patients and should inform patients about the need to restrict the use in time. HS use could also be decreased by computer based reminders regarding appropriate use ^[19]. Furthermore, a tapering scheme could be proposed to the patient, and implemented after the acute phase of illness, through electronic communication between the hospital and the community-based physicians. This could especially be the case for patients admitted to surgical wards, where immediate discontinuation is perhaps not suitable, but where evaluation of appropriate pharmacotherapy is not routinely applied. This action should be facilitated by the government through dissemination of guidelines for HS use and by setting up pilot projects in hospitals.

Several actions have already been taken in our hospital, including automatic stop orders in the electronic prescribing system for newly started HS use, clinical pharmacists' advice to lower HS doses in case patients are sleeping well and to change long-acting substances to intermediate

acting HSs (e.g. a clinical pharmacist has been attached to the ward of thoracic vascular and plastic surgery, and more surgical wards should be foreseen for clinical pharmacy in the future). Furthermore, a protocol for active cessation is being set up, using a fast withdrawal scheme over one week, for patients aged more than 55 years suffering from different pathologies ^[20,21].

CONCLUSION

The prevalence of HS use in our university hospital is high, mostly as a result of continuation of HSs that were started before admission. In comparison to ten years ago, HSs are started in fewer patients in the hospital, and when this is the case, the formulary guidelines are followed. There is still a long way to go to reduce the high consumption of HS, and strategies such as warnings through the electronic prescribing system, clinical pharmacy advice and active tapering and discontinuation schemes for targeted patients should be explored.

ACKNOWLEDGEMENTS

The authors are indebted to pharmacist F. Lavreau, for her valuable help with the data collection, to the participating heads of the medical departments, the head nurses and to the participating patients. This study was not funded and the authors have no conflicts of interest.

TABLES

Table 1: Demographic data of the participating patients (n=326)

	Females (n = 155)	Males (n = 171)	Total (n = 326)
Mean age (years) \pm SD	49.6 \pm 16.6	57.0 \pm 17.0	53.5 \pm 18.6
Median age (years)	48	62	55
Mean length of stay (days) \pm SD	16.9 \pm 29.2	21.1 \pm 34.0	19.1 \pm 31.8
Median length of stay (days)	8	10	9

Table 2: Number of patients, mean age, median length of stay (LOS) and percentage of HS users per ward during admission (n=326)

	Number of patients	Mean age (years)	Median LOS (days)	% of HS users
Abdominal surgery	17	62.1	13	52.9%
Cardiology	49	67.3	9	53.1%
Head and neck surgery	29	59.8	5	31.0%
Maternity	42	29.9	4	0.0%
Nephrology	42	58.0	9	42.9%
Plastic surgery	28	44.3	13.5	60.7%
Pneumology	43	54.4	8	30.2%
Psychiatry	15	48.5	39	73.3%
Rehabilitation	20	39.6	108	75.0%
Thoracic and vascular surgery	41	62.2	6	56.1%

Table 3: Incidence of HS use: comparison between the year 2000 and 2009

	2000	2009
Total number of patients	493	326
Patients using HSs before admission (interview)	143 (29.0%)	100 (30.7%)
Patients using HSs before admission (file)	N.A.	108 (33.1%)
Patients using HSs in the hospital (interview)	N.A.	108 (33.1%)
Patients using HSs in the hospital (file)	223 (45.2%)	141 (43.3%)
Newly started patients in the hospital (file)	100 (28.6%) (*)	34 (15.5%) (*)
Patients using HSs before admission that were discontinued in the hospital (file)	20 (14.0%) (**)	21 (19.4%) (**)
Patients using HSs after discharge (file)		58 (17.8%)

N.A.: not available

(*) percentage calculated on the number of patients who took no HS before admission

(**) percentage calculated on the number of patients who took a HS before admission

Table 4: Incidence of HS use during hospitalization, per ward

Ward	patients	HS users	%	>1 HS
Abdominal surgery	17	9	52.9	4
Cardiology	49	26	53.1	7
Head and neck surgery	29	9	31.0	3
Maternity	42	0	0	0
Nephrology	42	18	42.9	6
Plastic surgery	28	17	60.7	9
Pneumology	43	13	30.2	5
Psychiatry	15	11	73.3	9
Rehabilitation	20	15	75.0	9
Thoracic and vascular surgery	41	23	56.1	14
Total	326	141	43.3	66

REFERENCES

1. Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, Klassen TP, Witmans M (2007) The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med* 22: 1335-1350
2. Panneman MJ, Goettsch WG, Kramarz P, Herings RM (2003) The costs of benzodiazepine-associated hospital-treated fall injuries in the EU: a Pharmo study. *Drugs Aging* 20: 833-839
3. Holbrook AM, Crowther R, Lotter A, Cheng C, King D (2000) The diagnosis and management of insomnia in clinical practice: a practical evidence-based approach. *CMAJ* 162: 216-220
4. Tamblyn R, Abrahamowicz M, du BR, McLeod P, Bartlett G (2005) A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. *J Am Geriatr Soc* 53: 233-241
5. Petrovic M, Mariman A, Warie H, Afschrift M, Pevernagie D (2003) Is there a rationale for prescription of benzodiazepines in the elderly? Review of the literature. *Acta Clin Belg* 58: 27-36
6. Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE (2005) Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 331: 1169
7. Pelissolo A, Notides C, Lepine JP, Bisserbe JC (1999) Anxiolytic and hypnotic use by general hospital inpatients. The impact of psychopathology and general medical conditions. *Gen Hosp Psychiatry* 21: 79-86
8. Wancata J, Benda N, Lesch O, Muller C (1998) Use of anxiolytics and hypnotics in gynecological, surgical and medical departments of general hospitals. *Pharmacopsychiatry* 31: 178-186
9. Bell CM, Fischer HD, Gill SS, Zagorski B, Sykora K, Wodchis WP, Herrmann N, Bronskill SE, Lee PE, Anderson GM, Rochon PA (2007) Initiation of benzodiazepines in the elderly after hospitalization. *J Gen Intern Med* 22: 1024-1029
10. Stuffken R, van Hulten RP, Heerdink ER, Movig KL, Egberts AC (2005) The impact of hospitalization on the initiation and long-term use of benzodiazepines. *Eur J Clin Pharmacol* 61: 291-295
11. Belgian health surveys conducted in 1997, 2001 and 2004; www.iph.fgov.be/epidemiologie/crospl/hisnl/his04nl/hisnl.pdf. 2010.
12. Warie H, Petrovic M, Somers A, Mariman A, Robays H, Pevernagie D (2003) The use of hypnosedative drugs in a university hospital setting. *Acta Clin Belg* 58: 225-232
13. Howes JB, Ryan J, Fairbrother G, O'Neill K, Howes LG (1996) Benzodiazepine prescribing in a Sydney teaching hospital. *Med J Aust* 165: 305-308
14. Nakao M, Takeuchi T, Yano E (2007) Prescription of benzodiazepines and antidepressants to outpatients attending a Japanese university hospital. *Int J Clin Pharmacol Ther* 45: 30-35
15. Edwards C, Bushnell JL, Ashton CH, Rawlins MD (1991) Hospital prescribing and usage of hypnotics and anxiolytics. *Br J Clin Pharmacol* 31: 190-192
16. O'Reilly R, Rusnak C (1990) The use of sedative-hypnotic drugs in a university teaching hospital. *CMAJ* 142: 585-589
17. Halfens RJ, Lendfers ML, Cox K (1991) Sleep medication in Dutch hospitals. *J Adv Nurs* 16: 1422-1427

18. Saltvedt I, Spigset O, Ruths S, Fayers P, Kaasa S, Sletvold O (2005) Patterns of drug prescription in a geriatric evaluation and management unit as compared with the general medical wards: a randomised study. *Eur J Clin Pharmacol* 61: 921-928
19. Agostini JV, Concato J, Inouye SK (2008) Improving sedative-hypnotic prescribing in older hospitalized patients: provider-perceived benefits and barriers of a computer-based reminder. *J Gen Intern Med* 23 Suppl 1: 32-36
20. Petrovic M, Pevernagie D, Mariman A, van MG, Afschrift M (2002) Fast withdrawal from benzodiazepines in geriatric inpatients: a randomised double-blind, placebo-controlled trial. *Eur J Clin Pharmacol* 57: 759-764
21. Elliott RA, Woodward MC, Osborne CA (2001) Improving benzodiazepine prescribing for elderly hospital inpatients using audit and multidisciplinary feedback. *Intern Med J* 31: 529-535

Chapter 5-4: Evaluation of clinical pharmacist ~~advices~~ recommendations at the geriatric ward in a Belgian university hospital

Somers A, Robays H, De Paepe P, Van Maele G, Petrovic M. Evaluation of clinical pharmacist ~~advices~~ recommendations at the geriatric ward in a Belgian university hospital. Publication in progress.

ABSTRACT

Aim: To evaluate the type, acceptance rate and clinical relevance of clinical pharmacist ~~advice~~ recommendations for one hundred patients at the geriatric ward of the Ghent university hospital.

Methods: The clinical pharmacist recommended drug therapy changes ~~formulated advice~~ during a weekly two-hour visit, during a four month period. The ~~advice~~ recommendations were evaluated with regard to type, acceptance, prescribed medication and underlying drug related problem. Two clinical pharmacologists and two clinical pharmacists independently and retrospectively evaluated the clinical relevance of the ~~advice~~ recommendations and rated their own acceptance. For each patient, appropriateness of prescribing was assessed using the Medication Appropriateness Index (MAI), before and after the clinical pharmacist ~~advice~~-recommendations.

Results: The clinical pharmacist ~~formulated~~ recommended 304 ~~advice~~ drug therapy changes for 100 patients taking a total of 1137 drugs. The most common underlying drug related problems concerned incorrect dose, drug-drug interaction and adverse drug reaction which were most frequent for cardiovascular drugs, drugs for the central nervous system and drugs for the gastrointestinal tract. The most common type of ~~advice~~ recommendation concerned adapting the dose, and stopping or changing a drug. In total, 59.7% of the ~~advice~~ recommendations were accepted by the treating physician. The acceptance rate by the evaluators ranged between 92.4% and 97.0%. The mean clinical relevance of the ~~advice~~ recommendations was assessed as possibly important (53.4%), possibly moderate (38.1%) and possibly very important (4.2%). A low inter-rater agreement concerning clinical relevance between the evaluators was found: overall intra-class correlation coefficient was 0.36 and kappa-values ranged between 0.15 and 0.25. Summated MAI scores significantly improved after the pharmacist ~~advice~~ recommendations with mean values decreasing from 9.3 to 6.2 ($p < 0.001$).

Conclusion: In this study, the clinical pharmacist identified a high number of potential drug related problems in older patients but the acceptance of the pharmacotherapy ~~advice~~ recommendations by the treating physician was lower than by a panel of evaluators. This panel however rated most ~~advice~~ as possibly important and possibly moderate, with a low inter-rater reliability. As appropriateness of prescribing seemed to improve with decreased MAI scores, clinical pharmacy

services may contribute to optimisation of drug therapy in older inpatients.

Keywords: Clinical pharmacist, drug related problems, geriatric inpatients

INTRODUCTION

Clinical pharmacy is defined as the provision of patient oriented pharmaceutical care, with the goal to maximize drug efficacy and to minimize drug harm by preventing drug related problems ^[1]. In hospitals, clinical pharmacists are active on the wards, where they analyse the pharmacotherapy of the patients in relation to the medical and laboratory data. They ~~advise~~ recommend drug therapy changes to physicians and nurses ~~concerning changes in and follow-up of pharmacotherapy~~, and they answer questions about drugs.

Clinical pharmacy exists since many decades in North America and the United Kingdom. Since several years it has been introduced in most European countries. About ten years ago, clinical pharmacy pilot projects were started in Belgian university hospitals, and since a few years the Belgian government finances clinical pharmacy projects in about fifty hospitals. Many of these projects concern older patients, since drug consumption is high in these patients, and the presence of many drug related problems requires careful assessment of drug therapy. Clinical pharmacy was introduced at the geriatric ward in our hospital in view of the high rate of drug related hospital admissions and drug related problems during hospitalization ^[2,3].

The clinical and economic impact of clinical pharmacy have been addressed in many studies, and the value of clinical pharmacy has been proven both by improvement of clinical and economic outcomes ^[4-10]. This study took place at the time when there was not yet financial support by the government. Therefore, it was important to document the initial findings concerning type of ~~advices~~ recommendations and acceptance by the treating physicians in our hospital. Moreover, we intended to assess the clinical relevance of the pharmacist ~~advices~~ recommendations in view of the extension of clinical pharmacy to other departments in the hospital.

METHODS

Setting and study design

This observational monocentric study was performed at the geriatric ward (28 beds) of the Ghent University Hospital, Belgium, during a four month period (April – July 2006). Three geriatricians

were active on the ward, assisted by two junior physicians, and there was a six months rotation system for the supervision by the geriatricians. During the study period, the supervision was performed by one single geriatrician. The clinical pharmacist started the activities at the geriatric ward six months before the beginning of the study.

Clinical pharmacist activity

The clinical pharmacist attended the geriatric ward during a weekly two hours visit, and formulated pharmacotherapy ~~advices~~ recommendations according to a standardized working method, with consultation of the medical and nursing file and the laboratory values. At the time of the study, the medical file and the laboratory values were already available in the electronic patient file, but the nursing file (including the pharmacotherapy chart) was still a paper document. The pharmacist screened for eight types of underlying drug related problems per drug: incorrect dose, inappropriate drug choice, drug-drug interaction, adverse drug reaction, incorrect frequency or time of administration, incorrect route of administration, unnecessary use of the drug, and contra-indication. Also, the pharmacist screened for untreated indications. The ~~advices~~ recommendations were formulated by means of a standardized form which was put in the nursing file next to the pharmacotherapy chart. On the form, the drug related problem was mentioned (mostly with a short explanation e.g. the mechanism of a drug-drug interaction), as well as the pharmacotherapy ~~advice~~ recommendation. The next day, during their round, the geriatrician and the junior physician noted on the form whether they accepted the suggestion of the pharmacist. In case of non-acceptance, the reason for this was recorded. The rates of acceptance were coded as 'accepted', 'partially accepted' and 'not accepted'. An ~~advice~~ recommendation was rated as partially accepted e.g. if the pharmacist ~~advised~~ recommended to lower the dose of a drug and the drug was totally stopped, or if the pharmacist ~~advised~~ recommended to start a drug and this drug was initiated but at another dose than proposed. The pharmacist did not attend the ward round due to time restrictions, and since many other issues besides drug therapy were discussed during this round. Follow-up of the ~~advices~~ recommendations was done one day after the ward round by collecting the forms and by checking whether the pharmacotherapy regimen was altered. In case the acceptance was not noted or in case an accepted ~~advice~~ recommendation did not lead to a change in

pharmacotherapy, the pharmacist contacted the treating physician for clarification. Only the patients for whom ~~advices~~ recommendations were formulated and only pharmacist-initiated ~~advices~~ recommendations (not questions) were taken into account.

Panel evaluation

Four health-care professionals rated independently and retrospectively the clinical relevance of the ~~advices~~ recommendations and assessed their own acceptance rate. These evaluators were two clinical pharmacologists (one geriatrician and one emergency medicine physician), and two clinical pharmacists with more than three years of experience. The clinical relevance of the ~~advices~~ recommendations was assessed by a previously developed scale ^[11], with six levels of clinical relevance of the pharmacist ~~advices~~ recommendations ranging from 'not relevant', to 'possibly low relevance', 'possibly important relevance', 'possibly very important relevance', 'possibly life saving', and one level with 'adverse significance' (in case a non appropriate ~~advice~~ recommendation was given).

Appropriateness of prescribing

The Medication Appropriateness Index (MAI) scoring system was used for assessment of appropriateness of prescribing before and after the pharmacist's ~~advices~~ ^[12]. This method has been used frequently for measuring interventions to improve pharmacotherapy in older patients ^[6,7,13,14]. In this approach, each drug is evaluated as appropriate, marginally appropriate or inappropriate by ten weighted criteria, resulting in a score per drug and in a summated score per patient. Inappropriate ratings for criteria with a high weight generate the highest scores. In the original MAI, ten questions are posed per drug taken; these ten questions concern indication, effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and expense. In our approach, the question about expense was not taken into account. The second MAI was calculated based on the acceptance of the treating physician; this means that not accepted ~~advices~~ recommendations were not taken into consideration.

Data analysis

Patient data, drug therapy and clinical pharmacist ~~advices~~ recommendations were recorded into a MS Access database (version 2007). Statistical analysis was performed by using SPSS version 19. The inter-rater variability was assessed by the intraclass correlation coefficient (ICC), and by the kappa statistics, whereby raters were compared two by two. An ICC or kappa value of > 0.8 indicates nearly perfect inter-rater agreement, kappa values between 0.6 and 0.8 indicate substantial agreement and kappa values between 0.4 and 0.6 indicate moderate agreement. The difference in acceptance rate between the treating physician and the evaluators was analysed by the Paired-Samples t-test. A p-value < 0.05 was considered statistically significant. The difference in MAI scores before and after the ~~advice~~ recommendation was calculated by the Wilcoxon Signed Ranks Test.

RESULTS

Clinical pharmacist ~~advices~~ recommendations

The clinical pharmacist formulated pharmacotherapy ~~advices~~ recommendations for 100 patients (52 males and 48 females, with a mean age of 81.4 years (SD 6.65, median 82 years). Twenty-three patients came from a nursing home or from another hospital, and four patients died during the hospital stay. The 100 patients took in total 1137 drugs (mean 11.4 drugs, SD 3.36, median 11 drugs, min 4 – max 23), which were mainly cardiovascular drugs (25.4%), drugs for the central nervous system (21.8%), drugs for the gastro-intestinal tract (20.2%) and drugs for blood disorders (11.1%).

In total, the clinical pharmacist ~~formulated~~ recommended 304 drug therapy changes ~~advices~~, with a maximum of six ~~advices~~ recommendations per patient. Table 1 summarizes the most common underlying potential drug related problems, which concerned inappropriate dose (31%), drug-drug interaction (20%), adverse drug reaction (15%), and inadequate pharmaceutical form (10%). The most common types of ~~advice~~ recommendation were changing the dose (35%), stopping a drug (18%), changing a drug (14%), and changing the pharmaceutical form (9%). Examples of ~~advices~~

recommendations are given in Table 2. The pharmacotherapeutic drug classes that induced most frequently the drug related problems were cardiovascular drugs (32%), drugs for the central nervous system (26%), drugs for the gastro-intestinal tract (11%) and anti-infectives (10%).

Acceptance rates

Table 3 illustrates the acceptance rates by the treating physicians and by the four evaluators. The treating physicians (the supervising geriatrician and the junior physicians) accepted 53.3% and partially accepted 6.3% of the clinical pharmacist ~~advices~~ recommendations. The types of ~~advices~~ recommendations which were best accepted were monitoring therapy (93.8% accepted), changing the pharmaceutical form (85.7%), requests to determine the serum concentration (84.6%) and to stop the drug (69.8%); the types of ~~advices~~ recommendations that were the least accepted were changing the drug (62.5% not accepted), starting a drug (60.9%) and changing the dose (49.5%). Two of the 304 ~~advices~~ recommendations were not evaluated by all four evaluators due to lack of clinical information. The four evaluators fully accepted 86.1%, 87.4%, 86.8% and 79.8% of the ~~advices~~ respectively, and partially accepted 7.0%, 9.6%, 7.0% and 12.6% respectively.

Clinical relevance

The clinical relevance of the ~~advices~~ recommendations (Table 4) was mostly scored as 'possibly important' (58.6%, 68.5%, 43.4%, and 43.0% respectively with a mean of 53.4%), and 'possibly moderate' (40.1%, 24.8%, 43.7%, and 43.7% respectively with a mean of 38.1%). The assessment 'possibly very important' was not attributed by all evaluators (0.0%, 4.6%, 6.3% and 6.0% respectively, with a mean of 4.2%). No ~~advices~~ recommendations were designated to be of possible life saving clinical relevance. One ~~advice~~ recommendation (0.3%) was categorized as an ~~advice~~ recommendation with adverse significance by all the evaluators, since the pharmacist had made a mistake by suggesting treatment for hyperkalaemia instead of hypokalaemia. The overall intra-class correlation coefficient was 0.36 indicating a poor agreement between the raters. Looking at the ratings of the two clinical pharmacologists, the kappa value was 0.21 and comparing

the ratings of the two clinical pharmacists, the kappa value was 0.15.

MAI scores

The mean summated MAI scores decreased from 9.3 (SD 5.12, min 2.0 - max 36.5) before the advice recommendation to 6.2 (SD 4.00, min 0 - max 26.5) after the advice recommendation. This decrease was significant ($p < 0.001$). The criteria with the highest (most inappropriate) scores were drug-drug interactions, dosage, and right choice, both for the calculation before and after the clinical pharmacist advice recommendation. The lowest scores were found for duplication of therapy, indication and drug-disease interactions. All mean scores per criterion decreased after the pharmacist advices recommendations. The scores for drug-drug interactions and dosage obtained the highest improvement (decrease from 2.65 to 1.8 and from 2.05 to 1.22 respectively).

DISCUSSION

Strengths and weaknesses

This study was observational and monocentric. In addition, only one clinical pharmacist was involved. Therefore, the results should be extrapolated with caution. The patient characteristics and the types of drugs prescribed at the acute geriatric ward are probably comparable to other hospitals, but the prescribing rules and the working method of the physicians and pharmacists may differ between institutions. Also, the detection of DRPs and the advices recommendations that were provided could strongly depend on the experience of the clinical pharmacist involved. However, the pharmacist had extensive training in geriatric pharmacotherapy and used a systematic and evidence based approach for detection of drug related problems. Secondly, no clinical endpoints were taken into consideration, e.g. hospital readmissions, mortality, and quality of life, and there was no control group of patients. The design of the study is therefore a weakness and a randomised controlled design with analysis of outcomes on morbidity and mortality would have been preferable. However, it should be clear that studying this type of intervention is extremely difficult since the presence of the pharmacist him/herself can influence already the

pharmacotherapy, and since the clinical pharmacist ~~advices~~ recommendations can influence the pharmacotherapy of other patients. Since the minimal time investment of the clinical pharmacist (only two hours per week), such a design was not possible and it was not the aim of this study to assess the impact of the clinical pharmacist on clinical outcomes. In fact, we intended to evaluate the characteristics of the clinical pharmacist ~~advices~~ recommendations and whether these seemed relevant according to a panel of experts in pharmacotherapy.

A strength of this study is the relatively high number of patients that were included and ~~advices~~ recommendations that had been given in the four-month study period, given the limited available time per week. It should also be stated that many more ~~advices~~ recommendations were given, such as clarification of prescriptions and drug charts (e.g. in case doses were not mentioned), and ~~advices~~ recommendations concerning pharmaco-technical aspects (e.g. how to administer antibiotic infusions). These ~~advices~~ recommendations were not taken into account since they are covered now by the electronic prescribing system in our hospital. Furthermore, drug information without formulation of ~~advices~~ recommendations (e.g. a warning for a drug-drug interaction when none of the two drugs could be changed) was not included in the analysis. Another possible strength is the structured approach of the clinical pharmacist by using a list of potential drug related problems, and by calculation of the MAI scores.

Clinical pharmacist ~~advices~~ recommendations

In this study, the clinical pharmacist focused on the analysis of pharmacotherapy during hospital stay, not on medication history upon admission and not on information at discharge, meaning that only the inpatient drug therapy was analyzed. The acceptance rate of the clinical pharmacist ~~advices~~ recommendations was somewhat lower than what has been reported in other studies [9,13,15-17]. This could be explained by the fact that the pharmacist was not present at the time when the ~~advices~~ recommendations were considered by the treating physician and that no further discussion was possible. Spending more time at the geriatric ward would possibly lead to a better integration in the multidisciplinary team which might enhance the awareness for drug related problems.

We found that the acceptance rate by the four evaluators was higher than that by the treating physicians. The reason for non-acceptance was mostly found in the notes and non-acceptance was discussed later on with the treating physicians. Three main reasons for not accepting the clinical pharmacist ~~advices~~ recommendations were identified: 1) the ~~advice~~ recommendation, even if valuable according to evidence based medicine, was not taken into account because of the already precarious situation of the patient (in situations when the patient was very ill, the physician decided not to change drug therapy, because in this case the benefits outweighed the possible risk e.g. a drug with increased risk of QT-prolongation in combination with another drug was not stopped, since the physician decided that the possible benefit of the combination outweighed the risk); 2) the ~~advice~~ recommendation was not valuable enough according to the treating physician (e.g. dose reduction of an antibiotic or digoxin was not taken into account since there were no visible signs of toxicity); 3) the drug was initially started by another physician (e.g. a cardiologist or the general practitioner), and the treating physician did not want to interfere. It is clear that the four evaluators did not take the second and the third motivation into account, since these are overruled by a comprehensive pharmacotherapy approach (e.g. the dose of digoxin should not exceed 0.125 mg in elderly patients in view of the increased risk of toxicity, even if serum concentration levels are below the maximum value). However, the first motivation is valuable and can only be judged by the treating physician.

Clinical relevance

The majority of the ~~advices~~ recommendations were considered as having an important or moderate clinical relevance, meaning that the clinical pharmacist was able to detect potential drug related problems and to give adequate ~~advices~~ recommendations. However, little agreement was found between the raters, even between the two physicians and between the two pharmacists. This could be due to the fact that the raters were not experienced to rate a clinical pharmacist ~~advices~~ recommendations, and worked totally independently. This situation could have been improved by having a preliminary test phase. Similar low agreement rates were found in other studies, suggesting the difficulty for assessment of this type of intervention ^[13;18].

Another measure for clinical relevance was the decrease in MAI score. Although one aspect (expense) was not taken into account in our study, our finding was congruent with the findings of another study in Belgium, where MAI scores decreased in a randomized controlled trial with clinical pharmacist's interventions for geriatric patients [7].

CONCLUSION

This study demonstrates that a clinical pharmacist was able to detect a high number of drug related problems in older patients, working in a systematic way within limited time. Our results also suggest that the role of the clinical pharmacist for geriatric inpatients should be enlarged, since the majority of the ~~advice~~ recommendations were rated as possibly important, and since there was an improvement in the appropriateness of prescribing.

ACKNOWLEDGEMENTS

The authors are indebted to the participating geriatricians prof. dr. N. Van den Noortgate, dr. A. Velghe, dr. P. De Smet and dr. K. De Wilde, to head nurse H. Van Doninck, and to the patients of the geriatric ward. Furthermore we thank the clinical pharmacists (S. Deryckere and S. Mertens) for their evaluation of the ~~advice~~ recommendations. Useful comments for this manuscript were provided by Prof. dr. M. Bogaert. This study was not funded and the authors have no conflicts of interest.

TABLES

Table 1: Characteristics of the underlying drug related problems (n=304)

Type of drug related problem	Number (%)	Types of drugs concerned
Inappropriate dose	95 (31%)	Statins, protonpumpinhibitors, anti-infectives, hypnotics, ACE inhibitors, antit
Drug-drug interaction	62 (20%)	Antithrombotics, digoxin, anti-infectives, psycholeptics, psychoanaleptics
Adverse effect	46 (15%)	Diuretics, ACE inhibitors, corticosteroids, psychoanaleptics
Inadequate form	32 (11%)	Analgesics, psycholeptics
Unnecessary drug	22 (7%)	miscellaneous
Wrong drug choice	22 (7%)	Cardiovascular drugs (beta blockers, diuretics, digoxin, ACE inhibitors)
Inappropriate frequency or administration time	9 (3%)	Anti-infectives, calcium/vit D, statins
Underuse	8 (3%)	Calcium/vit D,
Contra-indication	5 (2%)	NSAIDs, antidiabetic drugs, antibiotics, beta blockers
Inappropriate route of administration	2 (1%)	Anti-infectives

Table 2: Examples of clinical pharmacist ~~advices~~ recommendations

Type of drug related problem	Drug	Advice Recommendation	Acceptation by treating physician
Recommendations Advices assessed as having possibly moderate clinical relevance (by all four evaluators)			
Unnecessary drug	Ranitidine 300 mg 1/day	Stop ranitidine, no concomitant drugs with corrosive effect on the gastric mucosa, reason for hospital admission not related with gastro-intestinal pathology	Accepted
Inappropriate dose	Simvastatine 40 mg 1/day	Lower dose to 20 mg 1/day since excellent cholesterol levels (TC 113 mg/dl, LDL 53 mg/dl), for woman 87 years old; no instable angina, no diabetes	Not accepted
Recommendations Advices assessed as having possibly important clinical relevance (by all four evaluators)			
Drug-drug interaction	Haloperidol 5 drops 3/day	Stop haloperidol due to interaction with amiodarone and domperidone: increased risk of QT-prolongation; consider to restart when domperidone therapy is stopped at 'if needed' frequency in case of agitation	Accepted
Wrong drug choice	Carvedilol 12.5mg 1/day	Patient with heart failure, ischemic heart disease, diabetes, COPD, receiving a.o. two beta blockers (nebivolol and carvedilol) but no ACE inhibitor; advice to stop carvedilol (non selective) and to start lisinopril 10 mg 1/day	Not accepted
Recommendations Advices assessed as having possibly very important clinical relevance (by two evaluators)			
Underuse	Calcium + vitamin D	Start calcium + vitamin D for woman, 83 years old, with known osteoporosis (and treatment with alendronate 70 mg weekly), now treated with methylprednisolone for several weeks	Accepted
Contra-indication	Nitrofurantoin 100 mg 2/day	Switch to other antibiotic because of decreased renal function (calculated GFR: 35 ml/min) (e.g. levofloxacin 500 mg 1 day, then 250 mg 1/day)	Accepted

TC: total cholesterol; LDL: low density lipoprotein; ACE: angiotensin converse enzyme inhibitor; GFR: glomerular filtration rate

Table 3 : Acceptance rates of the clinical pharmacist advice recommendations (n=302)

	Treating physician	Rater I Physician – clinical pharmacologist	Rater II Physician – clinical pharmacologist	Rater III Clinical pharmacist	Rater IV Clinical pharmacist
Accepted	53.6%	86.1%	87.4%	86.8%	79.8%
Partially accepted	6.3%	7.0%	9.6%	7.0%	12.6%
Not accepted	40.1%	7.0%	3.0%	6.3%	7.6%

Table 4: Clinical relevance of the clinical pharmacist advice recommendations (n=302)

	Rater I	Rater II	Rater III	Rater IV	Mean
1 - no clinical relevance	1.0%	1.7%	6.3%	7.0%	4.0%
2 - possibly moderate	40.1%	24.8%	43.7%	43.7%	38.1%
3 - possibly important	58.6%	68.5%	43.4%	43.0%	53.4%
4 - possibly very important	0.0%	4.6%	6.3%	6.0%	4.2%
5 - possibly life-saving	0.0%	0.0%	0.0%	0.0%	0,0%
6 - adverse significance	0.3%	0.3%	0.3%	0.3%	0,3%

REFERENCES

1. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm* 1990;47:533-543.
2. Somers A, Petrovic M, Robays H et al. Reporting adverse drug reactions on a geriatric ward: a pilot project. *Eur J Clin Pharmacol* 2003;58:707-714.
3. Somers A, Robays H, Vander SR et al. Contribution of drug related problems to hospital admission in the elderly. *J Nutr Health Aging* 2010;14:477-482.
4. Bond CA, Raehl CL, Franke T. Interrelationships among mortality rates, drug costs, total cost of care, and length of stay in United States hospitals: summary and recommendations for clinical pharmacy services and staffing. *Pharmacotherapy* 2001;21:129-141.
5. Brown BK, Earnhart J. Pharmacists and their effectiveness in ensuring the appropriateness of the chronic medication regimens of geriatric inpatients. *Consult Pharm* 2004;19:432-436.
6. Gillespie U, Alassaad A, Henrohn D et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Arch Intern Med* 2009;169:894-900.
7. Spinewine A, Swine C, Dhillon S et al. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. *J Am Geriatr Soc* 2007;55:658-665.
8. Kaboli PJ, Hoth AB, McClimon BJ et al. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med* 2006;166:955-964.
9. Kucukarslan SN, Peters M, Mlynarek M et al. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. *Arch Intern Med* 2003;163:2014-2018.
10. Holland R, Lenaghan E, Harvey I et al. Does home based medication review keep older people out of hospital? The HOMER randomised controlled trial. *BMJ* 2005;330:293.
11. Overhage JM, Lukes A. Practical, reliable, comprehensive method for characterizing pharmacist's clinical activities. *Am J Health Syst Pharm* 1999;56:2444-2450.
12. Hanlon JT, Schmader KE, Samsa GP et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992;45:1045-1051.
13. Stuijt CC, Franssen EJ, Egberts AC et al. Appropriateness of prescribing among elderly patients in a Dutch residential home: observational study of outcomes after a pharmacist-led medication review. *Drugs Aging* 2008;25:947-954.
14. Hanlon JT, Artz MB, Pieper CF et al. Inappropriate medication use among frail elderly inpatients. *Ann Pharmacother* 2004;38:9-14.
15. Spinewine A, Dhillon S, Mallet L et al. Implementation of ward-based clinical pharmacy services in Belgium--description of the impact on a geriatric unit. *Ann Pharmacother* 2006;40:720-728.
16. Bosma L, Jansman FG, Franken AM et al. Evaluation of pharmacist clinical interventions in a Dutch hospital setting. *Pharm World Sci* 2008;30:31-38.
17. Leape LL, Cullen DJ, Clapp MD et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA* 1999;282:267-270.
18. Buurma H, De Smet PA, Leufkens HG et al. Evaluation of the clinical value of pharmacist's modifications of prescription errors. *Br J Clin Pharmacol* 2004;58:503-511.

Chapter 4 5: Applicability of an adapted Medication Appropriateness Index (MAI) for detection of drug related problems in geriatric inpatients

This chapter is based upon:

Somers A, Mallet L, van der Cammen T, Robays H, Petrovic M. Applicability of an adapted Medication Appropriateness Index (MAI) for detection of drug related problems in geriatric inpatients. Am J Geriatr Pharmacother 2012 Feb 1, in press.

ABSTRACT

Background: High drug consumption in older patients and the presence of many drug-related problems require careful assessment of drug therapy, for which a structured approach is recommended.

Objective: To evaluate the applicability of an adapted version of the Medication Appropriateness Index (MAI) in 50 geriatric inpatients at the time of admission.

Methods: We reviewed for 432 prescribed drugs indication, right choice, dosage, directions, drug-disease interactions, drug-drug interactions and duration of therapy. Additionally, adverse drug reactions were evaluated, resulting in 8 questions per drug. MAI scores were attributed independently by a geriatrician and by a clinical pharmacist, and differences between them were assessed. Furthermore, the relationship between MAI score and drug-related hospital admission was explored.

Results: Mean summed MAI scores of 13.7 according to the geriatrician and 13.6 according to the pharmacist were obtained. The highest scores were found for drugs for the central nervous and the urinary tract system; the highest scores per question were detected for right choice, adverse drug reactions, and drug-drug interactions. A good agreement between the scores of the geriatrician and the pharmacist was found: intraclass correlation coefficient was 0.91 and overall kappa value was 0.71. A significantly higher MAI score was found for drug-related hospital admissions ($p=0.04$ for the geriatrician and 0.03 for the pharmacist).

Conclusions: This adapted MAI score seems useful for detection of drug-related problems in geriatric inpatients and reliable with a low inter-rater variability and positive correlation between high score and drug-related hospital admission. We consider further application of the adapted MAI for teaching and training of clinical pharmacists, and as a systematic approach for detection of drug-related problems by the clinical pharmacists in our hospital.

Keywords: Drug-related problems, geriatric inpatients, Medication Appropriateness Index

INTRODUCTION

Drug consumption in older patients is high, in part because of multiple patient co-morbidities. Furthermore, in combination with pharmacokinetic and pharmacodynamic changes, drug-related problems (DRPs) in older adults are common. Research has also shown that DRPs are responsible for a considerable proportion ($\pm 15\%$) of hospital admissions ^[1-6]. As a consequence, careful and thorough assessment of drug therapy in older people is necessary to prevent negative outcomes associated with DRPs.

Assessment of drug therapy in older adults is usually seen as evaluation of medication appropriateness. Several methods and instruments have been developed for this assessment, and are categorized as explicit (criteria-based) or implicit (judgment-based) approaches, or a combination of both ^[7-10]. Explicit criteria include lists of drugs to avoid or indicators for the appropriate prescribing for several drugs or diseases. Using an implicit approach means that clinical information of the individual patient is taken into account to judge appropriateness. In general, the combination of a structured approach and clinical judgment is recommended ^[7,11]. One such instrument is the Medication Appropriateness Index (MAI), developed in 1992 by Hanlon and colleagues, which was specifically developed to assess appropriateness of prescribing in older adults ^[12]. The original MAI required rating ten weighted explicit criteria for each drug prescribed, resulting in a score per drug and in a summated score per patient.

The MAI was originally used and tested in older outpatients, but over time has also been used in inpatient care and long-term care settings. Although the MAI has been tested in terms of reliability and validity ^[12], suggestions for improvement have been made ^[13], and some modified versions have been evaluated ^[14-16]. Working with the original MAI we encountered some problems that might be specific to our institution or to the prescribing procedures in our country, and we found some adaptations useful. It was not our goal to replace the original MAI index by a new version; we simply adapted the instrument to be a more feasible tool for systematic use in the hospital setting, as we found the MAI approach to be of particular value for pharmacotherapy evaluation in older patients. In our approach, adaptations of the questions were made in order to simplify the

instrument and to cover more aspects of drug therapy. In this study, our goal was to evaluate the applicability of an adapted version of the MAI in geriatric inpatients. We compared the MAI scores computed by a geriatrician and a clinical pharmacist and also explored the relationship between the MAI score and drug-related hospital admission, to evaluate whether inappropriate drug therapy was indeed reflected by the MAI score.

METHODS

Setting and study design

This retrospective, observational, single center study was performed in the geriatric ward of the Ghent University Hospital, Belgium. The selected patients were evaluated for the purpose of a study concerning adverse drug reactions as described elsewhere^[17] and agreement for exploration of drug use was obtained by written informed consent. Patients who were admitted to the geriatric ward between September 2008 and December 2008 were enrolled. Exclusion criteria were age younger than 65 years and unwillingness to participate in the study.

Data collection

Drug use at the time of admission, medical problems, and reason for hospitalization were recorded for 50 patients in an Access database (Microsoft Inc., Remond, WA, USA). Demographic data collected included age, gender, origin (home, nursing home, other hospital), and length of stay. All data were available in the electronic medical file and relevant laboratory data were also collected. For the drugs used at admission we recorded generic name, dosage, frequency, route of administration, and if possible, starting dates. DRPs at the time of admission were recorded and the contribution of the DRPs to hospital admission was assessed; DRPs that were the dominant reason for hospitalization, or that strongly or partly contributed to hospitalization were taken into account.

Adapted MAI score

In the original MAI, ten questions per drug taken are asked; these ten questions concern indication,

effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration, and expense. In our approach, three questions were not included (practical directions, duplication of therapy, and cost), one question was rephrased (i.e., effectiveness was changed into right choice), and one question about adverse drug reactions was added. The criteria of Hallas were used concerning the causality for adverse drug reactions ^[18]. The relative weight per question in the original MAI was partly changed (Table 1; original versus adapted MAI tool).

In order to evaluate content validity, a questionnaire with the five adaptations of the original MAI was sent to 8 experts in geriatric pharmacotherapy (4 geriatricians and 4 clinical pharmacists) from three different countries (Belgium, the Netherlands, Canada). The experts were asked to rate the relevance of the five adaptations on a 4-point scale (4 = very relevant, 3 = relevant, 2 = not very relevant, 1 = not relevant), and for the modified or new questions whether the question was clear (4-point scale). For each statement, the content validity index (CVI) was calculated (number of relevant ratings divided by the number of raters) ^[19] (Table 2; CVI per adaptation). For four of the adaptations, the CVI was above 0.85, which is considered as acceptance. Two experts did not find it opportune to leave out the question about costs, but because it was not our aim to define a cost perspective and to set forth criteria for interchangeable drugs at the generic level, we did not consider this omission important. Finally, the new question about adverse drug reactions was rephrased by adding that this concerned current or past adverse drug reactions.

Calculation of scores

As in the original MAI, scores were attributed to each question through multiplication of its weight by 0, 0.5, or 1, according to whether the drug was appropriate, marginally appropriate, or inappropriate respectively. This means that higher scores are obtained for more inappropriate drug therapy. The adapted MAI score was calculated independently by a geriatrician (MP) and by a clinical pharmacist with experience in geriatric medication review (AS). The two raters together tested the adapted MAI for five patient records (which were not included in the overall analysis), and during this preliminary test a procedure for each adapted MAI question was developed (i.e., no possible adverse drug reactions were considered; only existing adverse reactions for a given

patient). An independent pharmacist processed the data to calculate the MAI scores of the two raters and to calculate the differences between them. The results of the scoring were not dichotomized; the three possibilities (appropriate, marginally appropriate, or inappropriate) were compared between the two raters, resulting in nine combinations per question.

Statistical analysis

The data were imported into SPSS version 17 (SPSS, Inc., Chicago, IL, USA) for statistical analysis. The relationship between total MAI score per patient and number of drugs was evaluated by the Mann-Whitney U test, and the difference in total mean MAI score between the geriatrician and the clinical pharmacist was analysed by the paired samples t test. The inter-rater variability was assessed by calculation of the overall percentage of agreement (po%), the positive (p-pos), marginally (p-marg), and negative (p-neg) agreement for each question, as well as by calculation of the chance-adjusted agreement using the kappa statistics. The correlation between the MAI scores of the two raters was assessed by the intraclass correlation coefficient or ICC (in the case of a good correlation the ICC approaches the value 1). Finally, the influence of drug-related hospital admission on total MAI score was evaluated by the independent samples t test.

RESULTS

Of the 50 patients in this study (Table 3), 22 were men. The mean age of the sample population was 83 years (SD [standard deviation] 6.2, median 84 years) with a mean length of hospital stay of 21.3 days (SD 33.6, median 14 days, min 4 – max 215 days). The patients took a mean of 8.6 drugs (SD 4.2, median 8 drugs, min 2 – max 20 drugs). Of the 432 drugs in total, the five most important categories were cardiovascular drugs (34.3%), central nervous system drugs (14.4%), drugs for pain and inflammation (13.4%), respiratory tract drugs (10.6), and hormones (7.6%). For four patients a DRP was the dominant reason for hospitalization, while, for four other patients a DRP strongly contributed to hospital admission, and for three patients a DRP partly contributed to admission. Therefore, hospital admission was considered to be drug-related in 11 patients (22%). The mean summated adapted MAI score per patient obtained by the geriatrician was 13.7 (SD

16.8, median 9.5, min 0.5 – max 90.5), and for the pharmacist was 13.6 (SD 11.6, median 11, min 0.5 – max 67.5). The mean adapted MAI score per drug was 1.59 (SD 2.67) for the geriatrician and 1.58 (SD 2.12) for the pharmacist.

The highest scores (most inappropriate therapy) were found for drugs prescribed for the urinary tract system, for the central nervous system, and for pain and inflammation (Figure 1). Taking into account relative weights, the highest scores obtained per question were detected for adverse drug reactions, right choice, indication, and drug-drug interactions.

The number of drugs was significantly correlated with higher MAI scores ($p = 0.028$). Good agreement between the scores of the geriatrician and the clinical pharmacist was found (Table 4): the kappa values of the eight questions ranged between 0.54 and 0.77 and the overall (mean) kappa value was 0.71. We found the highest kappa values for drug-disease interactions (0.77), dosage (0.74), and adverse drug reactions (0.74), and the lowest values for directions (0.54) and indication (0.65). The highest consistency between the geriatrician and the pharmacist was found for appropriate ratings, with a positive agreement of 0.97; the agreement for inappropriate ratings was 0.57.

A non-significant difference in adapted MAI scores per drug between the geriatrician and the pharmacist was observed ($p = 0.864$ and 95% confidence interval [-0.14, 0.12]). However, the difference in MAI scores between the geriatrician and the pharmacist was significant for cardiovascular drugs and drugs prescribed for the central nervous system (p -values <0.001 and 0.014 respectively, data not shown in the table).

The ICC of the MAI scores by the geriatrician and the pharmacist was 0.91, which reflects a high inter-rater agreement. Finally, a significant higher MAI score was found for drug-related hospital admission ($p=0.04$ for the geriatrician and 0.03 for the pharmacist).

DISCUSSION

Adapted MAI instrument

With regard to the adapting the questions, we considered several issues. First, we omitted three questions: practical directions, duplication of therapy, and expense (cost).

- In previous tests, we encountered the difficulty that correct directions do not always correspond with practical directions for the patient. For example, more frequent administration can be correct in view of the pharmacokinetic properties but a once daily dosing schedule is more practical. Another example is that in case of hypertension or heart failure, it is better to prescribe conventional tablets than effervescent tablets (which can contain much sodium), but this can be impractical for a patient with swallowing problems. A second reason is that around 20% of the patients admitted to the geriatric ward in our hospital come from nursing homes (16% of patients in our sample), in which administration of drugs is managed by nursing home personnel, and factors such as frequency and pharmaceutical form, possibly leading to drug errors, become less important. However, the practicality of the drug scheme remains important and this was taken into consideration as much as possible after having looked for correct directions.
- Duplication of therapy was omitted because in our previous tests we found few double therapies in the strictest sense, for example, two benzodiazepines with the same indication, or twice the same medicine in which one was a generic and the other the original drug. However, we did encounter frequent situations in which several medicines from the same pharmacological class were combined for a possible beneficial effect (e.g., two diuretics, a medium long-acting and a short-acting benzodiazepine, and a short acting and a longer acting anticholinergic drug for inhalation). In our opinion, the distinction in duplicate therapy between a situation in which one drug is probably a mistake and inappropriate, and a combination used for a specific goal, is difficult to make. Moreover, when older patients are admitted to hospital it is not always possible to know the reasons for which a second medicine of the same class was added, in view of the fact that these were prescribed by different physicians. In the case of a true duplicate therapy, we agreed to categorise this into the question about drug-drug interactions.
- For the cost aspect, one has to define the cost perspective, i.e., the patient, hospital, or insurance organisation. This is difficult in Belgium, due to the complex system for reimbursement of drug costs during hospitalization. Some drugs are not reimbursed and are paid for by the patient (with a maximum however), some drugs are partly financed by the government with a fixed amount per hospital admission and partly by the hospital itself, and

some drugs are totally financed by the government. This complexity causes problems in defining the least expensive drug because this will differ according to which perspective is taken into account. Moreover, equivalent generic drugs can have different reimbursement regimens, which can rapidly change over time, making a cost analysis of equivalents arduous and with a time-limited validity. In addition, hospitals work with formularies, and physicians in our institution often automatically switch to formulary medicines when patients are admitted. At the time of our evaluation the switch between the medication scheme at admission and the continuation during hospitalization had not yet been electronically achieved and in the drug list at admission it was not always known if the patient took a generic drug, or which generic drug was prescribed.

Second, the question about effectiveness was rephrased into “Is the medication the right choice for the condition?” In the original MAI instructions, effectiveness was defined as producing a beneficial result. We found “right choice” more clear, in view of evaluating whether a prescribed drug is the right choice within a certain pharmacological class, and whether the potential risks of a drug outweigh the potential benefits.

Third, a question about adverse drug reactions was added: “Are there clinically significant adverse drug reactions?” We found this useful given the high proportion of older patients experiencing adverse drug reactions not only during hospital stay but also prior to admission and contributing to hospitalization. One can argue that adverse drug reactions occur at “normal” doses and are therefore not an element of inappropriate prescribing; however, we encountered situations while using the original MAI when patients experienced adverse reactions to drugs that were the right choice, not contra-indicated, prescribed at correct doses and with appropriate directions, and which were not due to drug-drug interactions. As older patients are more prone to the occurrence of adverse drug reactions because of changes in pharmacokinetic and pharmacodynamic properties, and because of decreased capability to handle drugs, it is important that adequate monitoring of adverse drug reactions be performed.

Adapted MAI scores

The mean summated patient scores were 13.7 (geriatrician) and 13.6 (pharmacist). The median

scores, however, were lower (9.5 and 11, respectively), meaning that drug therapy of only a relatively small group of patients was evaluated as inappropriate. When comparing the mean summated MAI score with those found in other studies, we can see that our results are similar [20-24].

Looking at the most frequently prescribed drug classes, we found that the highest scores (highest inappropriateness) were found for drugs of the central nervous system and for pain and inflammation. Examining the type of questions and taking into account the weights of the questions, we can conclude that the highest scores were attributed to adverse drug reactions and to right choice (both by the geriatrician and the pharmacist). Furthermore, the geriatrician obtained high scores for the question about indication, and the pharmacist for drug-drug interactions.

Two main findings in our study need to be considered. First, higher MAI scores for drug-related hospital admissions were found. This suggests that the adapted MAI we used could be useful in detecting clinically important drug-related problems. Second, a very good agreement between the scores of the geriatrician and the clinical pharmacist was obtained (overall kappa value of 0.71), indicating substantial inter-rater reliability. In other studies, overall kappa values obtained were mostly lower, and ranged from 0.47 to 0.83 [12,14-16,21,22]. Naturally, inter-rater variability depends on the differences in clinical background of the raters and their experience in MAI rating, and therefore the instructions, definitions, and preliminary testing beforehand are very important.

Usefulness of the adapted MAI

The original MAI index has been judged a valuable instrument for assessment of drug therapy appropriateness [7,20]. This is due to the fact that the MAI evaluates the prescribed drugs in several aspects. We changed the original MAI to enlarge these aspects with questions about adverse drug reactions and right choice, and we reduced the number of questions by grouping different aspects together (e.g., drug-drug interactions and duplication of therapy). We think that the instrument we used enables us to evaluate all aspects of pharmacotherapy in a systematic way, and the total scores obtained per drug allow us to set priorities for changes in drug therapy. More specifically, the higher the score of a given drug, the more reason there is to change or stop the drug. Alternatively, the total scores obtained per question can point to problem areas; for example, a

high score for the question about dose could reveal a problem of renal failure. This approach is of high value for clinical pharmacists in the detection of drug-related problems and the advice they should give to the geriatrician. Consequently, this adapted MAI could be useful in teaching pharmacists and physicians about clinical cases, and for training clinical pharmacists. Using the eight questions per drug is now recommended as a systematic approach for detection of drug-related problems by all clinical pharmacists in our hospital. Furthermore, this approach is useful for initiating discussion about pharmacotherapy between pharmacists and physicians, especially when questions arise about the right choice of a drug for a certain disease.

Strengths and weaknesses

The main strength of this study is the relatively high number of patient drug profiles that were scored (50 patients); in other studies, this number ranged from ten to thirty-two [12,15,16,21]. Furthermore, the inter-rater test period beforehand, the instructions for scoring that were developed, as well as access to accurate patient information via electronic medical files can be considered as strong points in our evaluation of the applicability of this adapted MAI version. An additional strength concerns the exploration of the relationship between MAI score and drug-related hospital admission, which allowed us to evaluate whether high MAI scores have indeed a clinical impact.

This study, however, has several weaknesses. First, it would have been valuable to test the *intra*-rater reliability in addition to the inter-rater reliability, by twice assessing the adapted MAI by the geriatrician and the pharmacist. Second, this was a single-centre study in which the geriatrician and pharmacist were used to collaborate, which could have over-estimated the inter-rater reliability. Finally, a supplementary question about undertreatment could have been added, in order to capture the situation in which the patient has a medical indication for therapy but is not receiving treatment.

CONCLUSION

The adapted MAI score seems useful for detecting drug-related problems in geriatric inpatients,

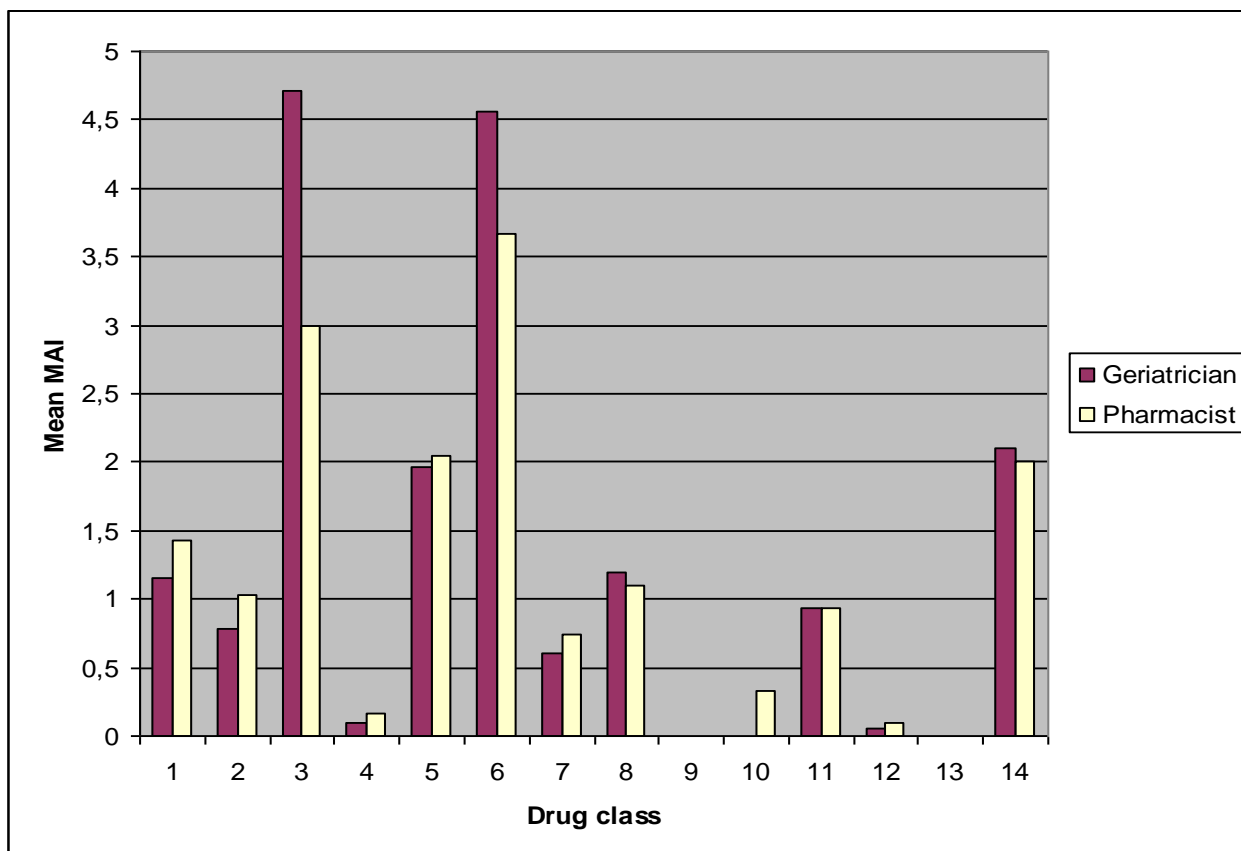
has a good inter-rater agreement, and a positive correlation between high score and drug-related hospital admission. We changed the original MAI index to cover more aspects of drug therapy and to reduce the number of questions by grouping certain aspects, but further research is needed to validate this instrument, preferably by experienced raters with a good clinical background. We consider further application of this adapted MAI for teaching and training of clinical pharmacists, and as a systematic approach for detection of drug-related problems by the clinical pharmacists in our hospital.

ACKNOWLEDGEMENTS

The authors are indebted to pharmacist E. Lonneville for her valuable help with the data collection. Furthermore we thank the geriatricians and the clinical pharmacists for their help in validating the adapted version of the instrument, and Prof. G. Van Maele for his advice in formulation of the statistical results. Useful comments for the final version of this manuscript were provided by Prof. M. Bogaert. This study was not funded and the authors have no conflicts of interest.

FIGURES AND TABLES

Figure 1: Mean MAI scores per drug class



(1) cardiovascular drugs, (2) gastro-intestinal drugs, (3) urinary tract system drugs, (4) respiratory tract drugs, (5) drugs for pain and inflammation, (6) central nervous system drugs, (7) hormones, (8) drugs for infections, (9) drugs for the immunity system, (10) anti-tumoral drugs, (11) minerals and vitamins, (12) dermatological drugs, (13) diagnostics (14) various drugs.

Table 1: Original versus adapted MAI index

Original MAI		Adapted MAI	
Question per drug	Weight	Question per drug	Weight
1. Indication	3	1. Indication	3
2. Effectiveness	3	2. Right choice	3
3. Dosage	2	3. Dosage	2
4. Correct directions	2	4. Directions	1
5. Practical directions	1	practical directions	
6. Drug-drug interactions	2	5. Drug-drug interactions	2
7. Drug-disease interactions	2	6. Drug-disease interactions	2
8. Duplication	1	duplication	
9. Duration	1	7. Duration	1
10. Expense	1	expense	
		8. Adverse drug reactions	2

(highest possible total score per drug: 18) (highest possible total score per drug: 16)

Table 2: Content validity index per adaptation with regard to the original MAI-index

Adaptation	Number of answers	Number of relevant findings (i)	CVI index (ii)	Comment
1. 'Is the medication effective for the condition?' was rephrased into 'is the medication the right choice for the condition?'	8	8	1	Considered as acceptance
2. The question 'Are the directions practical' was omitted and practicality of directions was – if possible – taken into account of the question about correct directions	8	8	1	Considered as acceptance; however, clarification of 'directions' was suggested (frequency, time of administration, route of administration, pharmaceutical form)
3. The question 'Is there duplication of therapy' was left out	7	6	0.86	Considered as acceptance
4. The question 'Is the drug the least expensive alternative compared to others of equal utility?' was left out	8	6	0.75	Considered as different opinions and no agreement; however we decided to leave the cost aspect out of the score in view of difficulties for the definition of the cost perspective and in view of the generic substitution to formulary drugs
5. A new question was added: 'Are there clinically significant adverse drug reactions'	8	7	0.86	Considered as acceptance; however clarification of 'clinically significant' was suggested (undesired symptoms or abnormal laboratory values with possible, probable or definite causality)

i. The answers considered as relevant findings were 'relevant' and 'very relevant' ('not relevant' and 'not very relevant' were not considered as relevant findings)

ii. CVI : content validity index = (number of relevant findings / number of answers); CVI values of > 0.85 are considered as acceptance in case of 8 raters

Table 3: Demographic data of the participating patients (n=50)

	Females (n = 28)	Males (n = 22)	Total (n = 50)
Mean age (years) ± SD	82.7 ± 6.8	83.5 ± 5.4	83.0 ± 6.2
Median age (years)	83	84	84
Mean length of stay (days) ± SD	27.2 ± 43.0	13.2 ± 6.9	21.3 ± 33.6
Median length of stay (days)	16	12	14
Mean number of drugs at admission ± SD	8.2 ± 4.3	9.2 ± 5.7	8.6 ± 4.6
Median number of drugs at admission	8	10	8

Table 4: Agreement between MAI scores of the geriatrician and the clinical pharmacist

Pharmacist	Geriatrician		
	Appropriate	Marginally appropriate	Inappropriate
Appropriate	A	B	C
Marginally appropriate	D	E	F
Inappropriate	G	H	I

Question	A	B	C	D	E	F	G	H	I	Kappa ^a	po (%) ^b	p-pos ^c	p-marg ^d	p-neg ^e
1. Indication	362	9	3	8	32	16	0	1	1	0.65	91.4	0.97	0.65	0.09
2. Drug-disease interactions	373	4	3	8	31	3	0	3	7	0.77	95.1	0.98	0.78	0.61
3. Right choice	356	12	1	8	35	9	0	2	9	0.72	92.6	0.97	0.69	0.60
4. Dose	357	1	3	16	39	2	1	6	7	0.74	93.3	0.97	0.76	0.54
5. Directions	384	5	7	8	12	1	1	10	4	0.54	92.6	0.97	0.50	0.30
6. Drug-drug interactions	263	14	1	15	73	1	10	26	29	0.69	84.5	0.93	0.72	0.60
7. Duration of therapy	351	5	2	5	18	13	1	10	27	0.72	91.7	0.98	0.52	0.68
8. Adverse drug reactions	315	3	6	18	52	5	2	10	21	0.74	89.8	0.96	0.74	0.65
Overall	2761	53	26	86	292	50	15	68	105	0.71	91.4	0.97	0.69	0.57

^a kappa = (observed agreement – possible agreement) / (1 – possible agreement)

^b po(%): overall percentage of agreement = $([A + E + I] / [A + B + C + D + E + F + G + H + I]) * 100$

^c p-pos: positive agreement = $(A * 2) / ([A + B + C] + [A + D + G])$

^d p-marg: marginal agreement = $(E * 2) / ([D + E + F] + [B + E + H])$

^e p-neg: negative agreement = $(I * 2) / ([G + H + I] + [C + F + I])$

REFERENCES

1. Beijer HJ, de Blaey CJ. Hospitalizations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 2002;24:46-54.
2. Mannesse CK, Derkx FH, de Ridder MA et al. Contribution of adverse drug reactions to hospital admission of older patients. *Age Ageing* 2000;29:35-39.
3. Kaiser RM, Schmader KE, Pieper CF et al. Therapeutic failure-related hospitalizations in the frail elderly. *Drugs Aging* 2006;23:579-586.
4. 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;50:1962-1968.
5. Pirmohamed M, James S, Meakin S et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-19.
6. Somers A, Robays H, Vander SR et al. Contribution of drug related problems to hospital admission in the elderly. *J Nutr Health Aging* 2010;14:477-482.
7. Shelton PS, Fritsch MA, Scott MA. Assessing medication appropriateness in the elderly: a review of available measures. *Drugs Aging* 2000;16:437-450.
8. Spinewine A, Schmader KE, Barber N et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet* 2007;370:173-184.
9. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing* 2008;37:673-679.
10. Barry PJ, O'Keefe N, O'Connor KA et al. Inappropriate prescribing in the elderly: a comparison of the Beers criteria and the improved prescribing in the elderly tool (IPET) in acutely ill elderly hospitalized patients. *J Clin Pharm Ther* 2006;31:617-626.
11. Kaur S, Mitchell G, Vitetta L et al. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. *Drugs Aging* 2009;26:1013-1028.
12. Hanlon JT, Schmader KE, Samsa GP et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992;45:1045-1051.
13. Spinewine A, Dumont C, Mallet L et al. Medication appropriateness index: reliability and recommendations for future use. *J Am Geriatr Soc* 2006;54:720-722.
14. Bregnhøj L, Thirstrup S, Kristensen MB et al. Reliability of a modified medication appropriateness index in primary care. *Eur J Clin Pharmacol* 2005;61:769-773.
15. Fitzgerald LS, Hanlon JT, Shelton PS et al. Reliability of a modified medication appropriateness index in ambulatory older persons. *Ann Pharmacother* 1997;31:543-548.
16. Kassam R, Martin LG, Farris KB. Reliability of a modified medication appropriateness index in community pharmacies. *Ann Pharmacother* 2003;37:40-46.
17. Onder G, Petrovic M, Tangiisuran B et al. Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: the GerontoNet ADR risk score. *Arch Intern Med* 2010;170:1142-1148.

18. Hallas J, Harvald B, Worm J et al. Drug related hospital admissions. Results from an intervention program. *Eur J Clin Pharmacol* 1993;45:199-203.
19. Polit DF, Beck CT. The content validity index: are you sure you know what's being reported? Critique and recommendations. *Res Nurs Health* 2006;29:489-497.
20. Spinewine A, Swine C, Dhillon S et al. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. *J Am Geriatr Soc* 2007;55:658-665.
21. Stuijt CC, Franssen EJ, Egberts AC et al. Reliability of the medication appropriateness index in Dutch residential home. *Pharm World Sci* 2009;31:380-386.
22. Hanlon JT, Artz MB, Pieper CF et al. Inappropriate medication use among frail elderly inpatients. *Ann Pharmacother* 2004;38:9-14.
23. Schmader KE, Hanlon JT, Pieper CF et al. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med* 2004;116:394-401.
24. Lund BC, Carnahan RM, Egge JA et al. Inappropriate prescribing predicts adverse drug events in older adults. *Ann Pharmacother* 2010;44:957-963.

Discussion and general conclusion

In this thesis five studies are presented providing information about the incidence and types of drug related problems in older hospitalized patients, and about a patient centred and pharmacist driven method to detect these problems in order to reduce clinical harm. There are several reasons why these studies were undertaken. Firstly, there is a demographic trend encompassing world wide aging, meaning that life expectancy is increasing and the proportion of older people is getting larger ^[1]. Since older people are the highest drug consumers, there is a need for special attention with regard to pharmacotherapy in this population. Secondly, a number of factors such as age related changes in pharmacokinetics and pharmacodynamics, multiple prescribers and polypharmacy contribute to a higher potential for drug related problems in older patients ^[2-5]. Thirdly, over the last years, there is increasing attention for development of clinical pharmacy in Belgian hospitals. In view of the need for specialised care for older persons, there is a possible role for the clinical pharmacist in detecting and preventing drug related problems for older hospitalized patients.

The general discussion first resumes the main findings of each study. After having considered the balance between limitations and strengths, ~~we addressed the added value of this work~~ recommendations for the future and for further research are addressed. Finally, ~~suggestions for further research~~ perspectives for further organization of clinical pharmacy in Belgium are formulated and key-elements which can be considered in other hospitals are highlighted.

1. Main findings

In the first study (Chapter 1), we assessed the incidence and types of Adverse Drug Reactions (ADRs) using two sources of reporting i.e. spontaneous reporting by physicians and nurses, and patient interviews by pharmacists. The study period lasted 8 months and 168 patients of the acute

geriatric ward were involved, whereby 56 patients were interviewed. ADRs with a possible and probable causality were considered and the severity of the ADRs was evaluated.

Main findings Chapter 1:

- Spontaneous reporting of ADRs by physicians and nurses revealed considerably less ADRs than patient interview by pharmacists. Physicians and nurses reported mostly the more serious adverse drug reactions that occurred during hospital stay, whereas the interviews revealed more ADRs that caused hospital admission.
- Adverse drug reactions occurred in 41% of the interviewed patients and for 19% of these patients an ADR was classified as serious, causing hospital admission. This confirms that ADRs are an important cause of hospital admission of geriatric patients, and occur frequently during their hospital stay.
- A correlation was found between taking drugs for the central nervous system or respiratory system and the development of a serious adverse drug reaction.

In Chapter 2, the incidence of drug related hospital admissions (DRHA) at an acute geriatric ward was studied. A broad definition of drug related problems, including overuse and underuse, was used. The study was an observational survey of 110 patients admitted during three non-consecutive months. Drug therapy was analyzed and the Beers' list was used to assess appropriateness of drug prescribing.

Main findings Chapter 2:

- For 20.9% of the patients, a DRP was dominantly (12.7%) or partly (8.2%) the reason for hospital admission. Adverse drug reactions and non-compliance were found to be the most important types of DRPs.
- The drugs most frequently causing a DRHA were drugs for the central nervous system.
- The incidence of DRHAs we found is higher than what has published in other studies; larger studies found lower incidences.
- We found no relationship between drug related hospital admission and intake of a drug listed in the Beers criteria for inappropriate drug use in the elderly.
- Patients admitted for a DRP took more drugs before admission than patients admitted because of other reasons.

In Chapter 3 the use of hypnosedative (HS) drugs at ten wards in our hospital was described, using patient interviews and exploration of the pharmaceutical file. In this study, 326 patients at ten different hospital wards were included. The results were compared with an observation period ten years before with 493 patients. Furthermore, the risk factors for use of HS drugs in our hospital were explored.

Main findings Chapter 3:

- The prevalence of HS use in our hospital is high: 33.1% according to the patient interview, and 43.3% according to the medical and nursing files.
- In 19.4% of the patients who took HSs before admission, their use was discontinued in the hospital. In 15.6% of the patients who took no HS before admission, a HS was started in the hospital, according to the formulary guidelines.
- There was a positive correlation between use of HSs in the hospital and older age, longer hospitalization, not coming from home, a higher number of HSs taken before hospitalization, sleeping problems emerging during hospitalization and CNS disorders respectively.
- In comparison with the previous registration period, we found a non-significant decrease in the use of HSs during hospitalization and a decrease in the number of newly started patients.

Chapter 5 4 comprised of an intervention study in which a clinical pharmacist formulated pharmacotherapeutic advices recommendations, during a weekly two-hour visit of the acute geriatric ward. The advices recommendations for 100 patients were evaluated in terms of number and types, underlying drug related problems and acceptance rate by the treating physician. The clinical relevance of the advices recommendations was assessed by a panel of four evaluators. Change in appropriateness of prescribing was assessed by calculating adapted MAI scores.

Main findings Chapter 5 4:

- The clinical pharmacist formulated a mean of 3 advices recommendations per patient, most frequently concerning incorrect doses, drug-drug interactions and adverse drug reactions. The drug related problems were mostly induced by cardiovascular drugs, drugs for the central nervous system and for the gastro-intestinal tract. The most common type of advice recommendation concerned adapting the dose, and stopping or changing a drug.
- In total, 59.7% of the advices recommendations were accepted by the treating physician. The acceptance rate by the panel of evaluators ranged between 92.4% and 97.0%.

- The mean clinical relevance of the ~~advices~~ recommendations was evaluated as possibly important (53.4%), possibly moderate (38.1%) and possibly very important (4.2%). A low inter-rater agreement concerning clinical relevance between the evaluators was found: overall intra-class correlation coefficient was 0.36.
- Summated MAI scores significantly improved after the pharmacist ~~advices~~ recommendations with mean values decreasing from 9.3 to 6.2 ($p < 0.001$).

In Chapter 4 5 we evaluated a systematic approach for detection of drug related problems in older patients, using an adapted version of the Medication Appropriateness Index (MAI) scoring system^[6]. Appropriateness of drug therapy at admission was assessed with this tool, for 50 patients hospitalized at the acute geriatric ward, independently by a geriatrician and a clinical pharmacist. For all drugs taken, 8 aspects were evaluated i.e. indication, drug-disease interactions, right choice, dose, directions, interactions, duration of therapy and adverse drug reactions. We also evaluated whether more inappropriate drug therapy would be associated with drug related admission.

Main findings Chapter 4 5:

- The most inappropriate ratings were found for drugs for the central nervous and the urinary tract system; the most inappropriate scores per question were detected for appropriate choice, adverse drug reactions and interactions.
- A good agreement between the scores of the geriatrician and the pharmacist was found: intra-class correlation coefficient was 0.91 and overall kappa-value was 0.71.
- A significantly more inappropriate MAI score was found for drug related hospital admission ($p=0.04$ for the geriatrician and 0.03 for the pharmacist).

2. Limitations of this research

An important limitation is the fact that the studies were performed solely in our institution, by a small group of researchers and a single clinical pharmacist. Moreover, all studies were carried out in a relatively short period of time. Although other issues arise in case of multicenter studies with different drug processes and multiple researchers, our approach could possibly limit generalisability of the findings^[7]. Lack of funding for this research and as a consequence lack of time due to other important projects for the pharmacy, led to constraints in performing studies on a

larger scale, including a higher number of older patients, and with a better support for data collection and analysis.

A second limitation concerns the fact that not all the processes in which drug related problems can occur were evaluated. We focused on drug related problems in older persons on admission during their hospital stay. Not all aspects of the pharmaceutical care process therefore have been evaluated. Other important domains are the pharmaceutical anamnesis at moments of transition (drug list upon admission, transfer, and discharge), the information to patients, the educational approaches for caregivers, and the role of the pharmacist in the design of computerized decision support systems, and in multidisciplinary team interventions ^[8]. In this work, information about drug related problems after hospitalization and interventions to prevent DRPs after discharge are lacking. Moreover, collaboration with primary caregivers was not addressed.

The most important limitation however is that, although a high incidence of DRPs was found in older patients, we did not study the impact of the pharmacist's interventions on health outcomes (morbidity, mortality, drug-related hospital readmissions), quality of life or cost-effectiveness. As shown in Chapter 5 4, there is evidence that pharmacotherapy for older patients can be optimized by the clinical pharmacist's interventions, but this remains a surrogate end-point which provides no information on clinical outcomes. Clinical pharmacists apply a patient centred approach to improve the outcome and safety of drug therapy, which is called the pharmaceutical care process. However, this process is a complex intervention which encompasses mainly medication review, but which also takes into account monitoring of drug therapy and patient follow-up. Interventions to optimise drug therapy must be adjusted to the clinical situation and to the needs of the individual patient. Moreover, when giving advice about drug therapy, clinical pharmacists cooperate with physicians and nurses and the proceeding is thus dependent on this cooperation. Therefore, it will be difficult to define, develop, document and reproduce these interventions, in comparison to clinical trials focussed on one single drug or drug class ^[9,10].

3. Strengths of this research

A first strength is that with our working methods, we were able to detect many drug related problems in older hospitalized patients. Although we have only studied what happened in our hospital, it is very likely that the issue of drug related problems in older patients is of concern in other institutions as well and that interventions to prevent drug related problems in older people are useful. We have also seen that multidisciplinary in-depth analysis, preferably with electronic data, reveals higher incidences of DRPs, because of more accurate recording of drugs and symptoms based on medical, nursing and laboratory findings. Furthermore, this information is useful for raising the awareness of physicians and nurses about the burden and types of DRPs in older patients and to enhance strategies for optimisation of drug treatment. One of these strategies includes regular medication review. In particular, attention should be paid ~~for~~ to the use of drugs for the central nervous system in older patients. Mainly hypnotic drugs are largely used, ~~as well~~ before, during and after hospitalization.

Secondly, we have demonstrated that a standardized approach for assessment of appropriateness of drug therapy in older patients seems useful. We invested time in the development of the registration forms for interview of patients in order to detect ADRs, in the method for assessment of drug related hospital admissions, and in the adaptation of the MAI score for feasible in hospital use. Since clinical pharmacy is expanding in our country, we consider further application of these tools for teaching and training of starting clinical pharmacists, and as a systematic approach for detection of drug related problems by the clinical pharmacists in our hospital. One can argue that the causality assessment of ADRs, the relevance of DRPs, and the contribution of a DRP to hospital admission, is a rather subjective interpretation of the rater, depending on the rater's own clinical experience and background. Therefore, we believe that using a standardized approach is of high value and almost necessary for the adequate detection and evaluation of DRPs. Furthermore, it is clear that drug therapy should be reviewed in-depth, by having full access to anamnesis results, medical records, laboratory values and nursing notes.

Finally, and most importantly, we have shown that the clinical pharmacist identified many drug related problems in the different studies. We have seen that the pharmacist reported more ADRs

than the physicians and the nurses, that intensive evaluation of drug therapy shows a high incidence of drug related hospital admission, and that a high number of pharmacotherapeutic advices were formulated. Several reasons can explain why the pharmacist retrieved many DRPs. A first reason is that pharmacists are trained to check drug therapy in order to prevent prescribing errors leading to clinical harm. Everyday in the pharmacy, prescriptions are checked and double-checked and the process of drug dispensing and preparation is performed within the concept of 'zero error tolerance'. In doing so, the pharmacists take their responsibility towards a safe drug process. Secondly, the high incidence of DRPs may be due to the fact that the geriatricians were not always able to review drug therapy for their patients, probably due to heavy work load, and possibly because adverse events were not recognized as related to medications. In our experience, it is a well known problem that physicians sometimes tend to minimize the needs for changing drug therapy, because this is not always their highest priority. However, as stated before, hospital admission of older patients could be the ideal moment for medication review, and the clinical pharmacist could advice the geriatrician in this matter. Furthermore, information towards general practitioners could be given. This leads us to conclude that the pharmacist could play a proactive role in the optimisation of drug therapy in older persons, which was confirmed with our finding that there was a positive impact on appropriateness of prescribing.

4. Recommendations for the future and for further research

Based on the findings of this doctoral thesis, we can make ~~several~~some recommendations for the future.

A first recommendation concerns the documentation of potential drug related problems and medication related harm. Even when causality is doubted, it can be worthwhile to document that certain problems can be due to certain drugs; this can be explored further on by physicians and pharmacists leading possibly to changes in drug therapy. A more accurate recording of adverse drug reactions and drug related hospital admissions, as well as the changes in drug therapy, could provide useful information in discharge letters and are useful when patients are readmitted. Therefore, we recommend that physicians, pharmacists, but also nurses would note questions and

findings about potential and probable drug related problems. As for clinical pharmacists, documentation of pharmacotherapeutic advice in the patient file is an essential point.

Another recommendation is that the search for optimization of drug therapy in older people should be enlarged by other elements, such as avoiding discrepancies in drug lists at the moments of transition, providing information to patients, setting up educational sessions for caregivers (e.g. nurses), helping in the design of computerized decision support systems, and participating in multidisciplinary team interventions ^[11,12].

Finally, efforts should be made to study more extensively the role of the clinical pharmacist in optimizing drug therapy for older people. Pharmacists directly involved in patient care for the elderly are scarce in hospitals and other health care settings in Belgium. The past few years we have seen an increase in their number, but there is still much scepticism about their added value. In our opinion, hospital pharmacists with postgraduate clinical knowledge and training are best suited to perform pharmaceutical anamnesis and medication review. However, for pharmacists to make a difference in patient care and medication management, we believe that physicians, pharmacists, and nurses should work together as a team, which can be accomplished relatively easy in the hospital setting. Moreover, pharmacists need to be able to have contact with the patient, in order to individualize drug therapy. This kind of approach should be evaluated in larger scale multicenter studies involving a higher number of clinical pharmacists and geriatricians, with evaluation of effects on not only appropriateness of prescribing but also on clinical outcomes such as hospital readmissions, mortality, and quality of life ^[13,14]. The time investment of clinical pharmacists while performing medication reviews and giving pharmacotherapeutic advices and the analysis of the cost-effectiveness is also a major issue ^[15].

5. Perspectives

5.1. Further organization of clinical pharmacy Belgium

In the research presented, the clinical pharmacist worked within a limited amount of time, and as mentioned above, this resulted in relatively small studies without assessment of impact on clinical

outcomes. Moreover, the pharmacist focused on evaluation of prescribing process and there are other elements which should be addressed in optimizing drug therapy for older inpatients. The question arises how clinical pharmacy should then be organized to be most efficient and to cover all these elements.

Of course full-time clinical pharmacy positions at each hospital ward would be ideal to cover all patients and all aspects, but this is not reasonable in view of the legally limited number of hospital pharmacists per number of beds. Moreover, there is another important aspect which is not in favour of full-time clinical pharmacy, namely routine tasks within the pharmacy itself remain necessary to maintain good knowledge about the drug process, formulary changes and work procedures, and to stay up to date with making standardized preparations.

Concerning strategic planning of clinical pharmacy services, we believe that the following elements are important:

- Introduction of electronic prescribing enhances clinical pharmacy activities, and there can be a shift from pharmacists implementing the electronic prescribing system towards pharmaceutical care once this implementation has been achieved.
- Education of pharmacy technicians for structured drug anamnesis; this can serve as a starting point for medication review by clinical pharmacists.
- Implementation of central clinical pharmacy activities for anti-infectives and nutrition, whereby recommendations can be given using a daily monitoring of electronic prescriptions within the pharmacy itself.
- Identification of key-wards which should be targeted first to set up clinical pharmacy services.
- Central monitoring of hospital wards without clinical pharmacy services, through validation of electronic prescriptions.

Furthermore, in order to avoid selected clinical pharmacy positions, we believe it is more motivating to allow different hospital pharmacists to provide clinical pharmacy services, at different

hospital wards (and day clinics). This is also favourable for exchange of information and to make teams in order to guarantee continuity in the future.

5.2. Key-elements which can be considered in other hospitals

Out of this research, several elements could be useful for implementation in other hospitals:

- There is a need for focused attention about drug related hospital admissions of older patients;
- Clinical pharmacists should perform medication review for older patients with polypharmacy (e.g. five or more medicines) and with drugs for the central nervous system;
- A structured approach for assessment of medication appropriateness should be used (e.g. with the adapted MAI criteria);
- Drug related problems (Adverse Drug Reactions, inappropriate doses, drug-drug interactions...) should carefully be reported in the patient file;
- Efforts should be made to convince patients taking hypnotic drugs to taper and eventually stop treatment;
- Clinical pharmacists should play an active role in the detection of drug related problems and should make recommendations to other caregivers to optimize drug therapy for older people.

Briefly, hospital pharmacists are not only responsible for getting the right drug to the right patient, but also for the correct administration of drugs, and for the outcomes of that drug use. In view of the high risk of drug related problems in older patients, the need for appropriate drug therapy is certainly required for this group of patients. We hope to have contributed in this work to the increased awareness of adverse drug-related issues in older patients. Attention for appropriate drug therapy for older patients is crucial and clinical pharmacists should play an active role in the detection and prevention of drug related problems in order to improve patient care.

6. References

1. Department of Economic and Social Affairs - Population Division. World Population Ageing: 1950 - 2050. United Nations . 2002.
2. Schwartz JB. The current state of knowledge on age, sex, and their interactions on clinical pharmacology. *Clin Pharmacol Ther* 2007;82:87-96.
3. Le Couteur DG, Hilmer SN, Glasgow N et al. Prescribing in older people. *Aust Fam Physician* 2004;33:777-781.
4. Barat I, Andreasen F, Damsgaard EM. Drug therapy in the elderly: what doctors believe and patients actually do. *Br J Clin Pharmacol* 2001;51:615-622.
5. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57:6-14.
6. Hanlon JT, Schmader KE, Samsa GP et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992;45:1045-1051.
7. Edwards SJ, Braunholtz DA, Lilford RJ et al. Ethical issues in the design and conduct of cluster randomised controlled trials. *BMJ* 1999;318:1407-1409.
8. Hepler CD. Pharmaceutical care. *Pharm World Sci* 1996;18:233-235.
9. Kaboli PJ, Hoth AB, McClimon BJ et al. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med* 2006;166:955-964.
10. Spinewine A, Schmader KE, Barber N et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet* 2007;370:173-184.
11. Gurwitz JH, Rochon P. Improving the quality of medication use in elderly patients: a not-so-simple prescription. *Arch Intern Med* 2002;162:1670-1672.
12. Kaur S, Mitchell G, Vitetta L et al. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. *Drugs Aging* 2009;26:1013-1028.
13. Holland R, Desborough J, Goodyer L et al. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol* 2008;65:303-316.
14. Castelino RL, Bajorek BV, Chen TF. Targeting suboptimal prescribing in the elderly: a review of the impact of pharmacy services. *Ann Pharmacother* 2009;43:1096-1106.
15. Schumock GT. Methods to assess the economic outcomes of clinical pharmacy services. *Pharmacotherapy* 2000;20:243S-252S.

Summary

Medication use is very common in older people for treatment and prevention of different diseases. Although there is evidence for improvement in health, drugs can also cause adverse events and especially older people are at risk for the development of drug related problems (DRPs). The overall aim of this research was to evaluate the incidence and types of drug related problems occurring in older hospitalized patients, and to assess the role of the clinical pharmacist in their detection and prevention.

Adverse drug reactions (ADRs) are an important cause of hospital admission of geriatric patients, and occur frequently during their hospital stay. Physicians and nurses tended to report the more serious ADRs that occur during hospitalization, and patient interview revealed more ADRs that caused hospital admission. A high incidence of drug related hospital admissions (DRHAs) was found using a broad definition of DRPs and a thorough analysis. The drugs most frequently causing DRHA were not listed in criteria for inappropriate drugs in older adults, and seemed to be drugs for the central nervous system. Hypnotosedatives (HSs) seemed to be widely used, as well before as during hospitalization. HSs that were started before admission were mostly continued in the hospital. A positive correlation between use of HSs in the hospital and older age, longer hospitalization and not coming from home was detected. A systematic approach for detection of drug related problems in older patients was evaluated, which was used by the clinical pharmacist in order to formulate pharmacotherapeutic recommendations ~~advices~~. Since there was a positive impact on appropriateness of prescribing, this leads us to conclude that the pharmacist could play a proactive role in the optimisation of drug therapy in older persons.

In conclusion, this dissertation has shown that drug related problems represent a major issue in older hospitalized patients, which makes careful evaluation of drug therapy necessary. The opportunities for clinical pharmacists using a systematic approach for detection and prevention of drug related problems were brought into view, and the role of the clinical pharmacist in optimizing drug therapy for older people was shown to be effective. Future studies should look especially look at the effect of clinical pharmacy services on clinical and economic outcomes.

List of publications

A. Publications related to the subject

1. Scientific publications in peer-reviewed journals

- Somers A, Petrovic M, Robays H et al. Reporting adverse drug reactions on a geriatric ward: a pilot project. Eur J Clin Pharmacol 2003;58(10):707-714
- Warie H, Petrovic M, Somers A, Mariman A, Robays H, Pevernagie D. The use of hypnotic sedative drugs in a university hospital setting. Acta Clin Belg 2003;58:225-32
- Somers A, Robays H, Vander Stichele R, Van Maele G, Bogaert M, Petrovic M. Contribution of drug related problems to hospital admission in the elderly. J Nutr Health Aging 2010;14:475-82
- Verrue C, Mehuys E, Somers A, Van Maele G, Remon JP, Petrovic M. Medication administration in nursing homes: pharmacists' contribution to error prevention. J Am Med Dir Assoc 2010;11(4):275-83
- Onder G, Petrovic M, Tangiisuran B, Meinardi MC, Markito-Notenboom WP, Somers A, Rajkumar C, Bernabei R, van der Cammen TJ. Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: the GerontoNet ADR risk score. Arch Intern Med 2010;170(13):1142-8
- Somers A, Robays H, Audenaert K, Van Maele G, Bogaert M, Petrovic M. The use of hypnotic sedative drugs in a university hospital: has anything changed in 10 years? Eur J Clin Pharmacol 2011;67(7):723-9

2. Scientific publications in national journals and chapters in books

- Somers A, Mehuys E, Petrovic M. Klinische farmacie: de rol van de apotheker in de farmacotherapie. Tijdschrift voor Geneeskunde 2007;63:669-671
- Somers A, Petrovic M, Vander Stichele R. Bijblijven 2007, nr 8: Farmacotherapie bij ouderen
- Petrovic M, Somers A, Vander Stichele R. Polyfarmacie bij de oudere patiënt. Tijdschrift voor Geneeskunde 2008;64:795-798
- Petrovic M, Somers A. De patiënt met bijwerkingen door medicatie. In: Olde Rikkert M, Flamaing J, Petrovic M, Schols J, Hoefnagels W, ed. Probleemgeoriënteerd denken in de geriatrie. Utrecht: De Tijdstroom uitgeverij, 2008, 357-371

3. Abstracts presented at international congresses

- Somers A, Petrovic M, Robays H, Bogaert M, Van Bortel L. Drug related problems leading to hospitalisation of geriatric patients. European Union of Geriatric Medicine Society congress, Vienna, September 2004. Poster presentation.
- Mallet L, Somers A, Guignard B. Managing drug interactions in the elderly. European Society of Clinical Pharmacy congress, Edinburgh, May 2007. Workshop.
- Somers A, Petrovic M, Robays H, Bogaert M, Van Bortel L. Clinical pharmacy activities at a geriatric ward: a pilot project. European Union of Geriatric Medicine Society congress, Frankfurt, September 2007. Poster presentation.
- Mallet L, Somers A. Systematic approach for medication review in the elderly. European Society of Clinical Pharmacy congress, Dubrovnik, October 2008. Workshop.
- Somers A, Petrovic M. Clinical pharmacy advises in a case of polypharmacy. European Society of Clinical Pharmacy congress, Dubrovnik, October 2008. Oral presentation.

- Somers A, Robays H, Petrovic M. Use of hypnotosedatives before and during hospitalization – comparison with a previous study from the year 2000. European Union of Geriatric Medicine Society congress, Dublin, September 2010.
- Somers A, Robays H, Petrovic M. Applicability of an adapted Medication Appropriateness Index (MAI) for detection of drug related problems in hospitalized elderly patients. European Society of Clinical Pharmacy congress, Lyon, October 2010. Oral presentation.
- Somers A. Medication review in the elderly. European Society of Clinical Pharmacy Symposium Geriatrics, Utrecht, May 2011. Workshop.

B. Publications not related to the subject

1. Scientific publications in peer-reviewed journals

- Somers A, Bauters T, Robays H et al. Evaluation of human albumin use in a university hospital in Belgium. Pharm World Sci 2002;24(3):111-116.
- Struys M, Somers A, Van Den Eynde N et al. Cost-reduction analysis of propofol versus sevoflurane: maintenance of anaesthesia for gynaecological surgery using the bispectral index. Eur J Anaesthesiol 2002;24(3):727-734.
- Colpaert K, Claus B, Somers A, Vandewoude K, Robays H, Decruyenaere J. Impact of computerized physician order entry on medication prescription errors in the intensive care unit: a controlled cross-sectional trial. Crit Care 2006;10(1):R21.
- Vander Stichele R, Van de Voorde C, Elseviers M, Verrue C, Soenen K, Smet M, Petrovic M, Chevalier P, Defloor T, Mehuys E, Somers A, Gobert M, De Falleur M, Bauwens M, Christiaens T, Spinewine A, Devriese S, Ramaekers D. Geneesmiddelengebruik in de Belgische rusthuizen en rust-en verzorgingstehuizen. Federaal Kenniscentrum voor de gezondheidszorg, 2006.
- Verrue C, Petrovic M, Mehuys E, Boussey K, Somers A, Spinewine A, Bauwens M, Gobert M, Elseviers M, Vander Stichele R. Organization of the medication management process in Belgian nursing homes. J Am Med Dir Assoc 2011;12(4):308-11.

2. Abstracts presented at international congresses

- Somers A, Natsch S, Salvezen-Blix H, Wöber E. Use of antibiotics in ambulatory respiratory tract infections. European Society of Clinical Pharmacy congress, Basel, October 2000. Workshop.
- Somers A, Buyle F, Van Hooreweghe M, Robays H. Evaluation of the quality of drug distribution in a university hospital. European Society of Clinical Pharmacy congress, Firenze, October 2002. Poster presentation.
- Somers A, Van Hooreweghe M, Vandenbroucke J, Robays H. Spontaneous reporting of medication errors and active observations of the drug process: results 2006. European Society of Clinical Pharmacy congress, Edinburgh, May 2007. Poster presentation.